MENTAL DISORDERS IN THE ELDERLY
A POPULATION STUDY IN 85-YEAR-OLDS

by

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MENTAL DISORDERS IN THE ELDERLY.
A POPULATION STUDY IN 85-YEAR-OLDS

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The prevalence of mental disorders and their relation to white matter lesions in the brain was studied in a representative sample of 85-year-olds (n=494) living in Gothenburg, Sweden. An extensive investigation including a psychiatric interview, interview of a close informant, a neuropsychological examination and computed tomography of the head was performed as part of the gerontological and geriatric population studies in Gothenburg, Sweden (H70).

I. The prevalence of dementia was 30% and of any other mental disorder 24%. Psychotic disorders were present in 5%, depressive disorders in 13%, and anxiety disorders in 11%. Forty-three per cent (43%) of all subjects, and significantly more women, used a psychotropic drug (men 30%, women 48%, p<0.001). Only one-fifth of those with depressive disorders received antidepressant drug therapy and one-tenth of those with psychotic disorders received neuroleptics. Only 1% of subjects with no psychiatric diagnosis were institutionalised, compared with 3% of those with other mental disorders and 48% of subjects with dementia. The institutionalisation rate was higher in more severe forms of dementia and in vascular dementia.

II. Psychotic syndromes and the subgroup schizophreniform syndrome were significantly more common in subjects with severe stages of dementia, mainly of Alzheimer's type, than in non-demented subjects. Depressive disorders were significantly more common in mild dementia than in non-demented subjects.

III. The percentage distribution of types of dementia was Alzheimer's disease 44%, vascular dementia 47% and other forms 10%. The three-year mortality was 23% in non-demented subjects, 42% in persons with Alzheimer's disease and 67% in those with vascular dementia. Infarcts visualised by computed tomography (CT) were significantly more common in demented than in non-demented subjects (28% vs 13%, p<0.01).

IV. The prevalence of white matter lesions (WMLs) was 69% in demented subjects, and 34% in non-demented (p<0.001). A stepwise logistic regression analysis showed that WMLs (p<0.001) and infarcts on CT (p<0.05) were independently associated with dementia. Non-demented subjects with WMLs scored significantly lower in several cognitive tests, especially those measuring spatial ability and perceptual speed, than non-demented subjects without such lesions. Demented subjects with WMLs scored significantly lower in tests measuring spatial ability and some aspects of memory than demented subjects without such lesions.

Key words: dementia, Alzheimer's disease, vascular dementia, epidemiology, prevalence, cerebral infarction, mortality, computed tomography, epidemiological methods, comorbidity, mental disorders, white matter lesions, psychometric testings, aged, population study

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<table>
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<th>Abbreviation</th>
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<tr>
<td>AD</td>
<td>Alzheimer's disease</td>
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<tr>
<td>ADL</td>
<td>Activities of daily living</td>
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<td>CAA</td>
<td>Cerebral amyloid angiopathy</td>
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<td>CBF</td>
<td>Cerebral blood flow</td>
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<td>DSM-III-R</td>
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<td>ECG</td>
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<td>GAD</td>
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<td>Health survey of 70-year-old people in Göteborg</td>
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<td>IS</td>
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<td>MDS</td>
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<td>MID</td>
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<td>MRI</td>
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<td>PDD</td>
<td>Primary degenerative dementia</td>
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<td>Senile dementia of Alzheimer's type</td>
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<td>Senile plaques</td>
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<td>TIA</td>
<td>Transitory ischemic attack</td>
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<td>WAIS</td>
<td>Wechsler Adult Intelligence Scale</td>
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<td>WHO</td>
<td>World Health Organisation</td>
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<td>VaD</td>
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This thesis is based on the following papers which will be referred to in the text by their Roman numerals.


AIMS OF THE STUDY

1) To study the prevalence of dementia and other mental disorders and the use of psychotropic drugs in a representative sample of 85-year-olds (Papers I and II).

2) To study the prevalence of functional mental disorders in demented 85-year-olds (Paper III).

3) To study the proportions of different types of dementias with a detailed clinical examination (Paper I).

4) To study white matter lesions on CT in relation to
   a) the prevalence of dementia (Paper IV)
   b) the prevalence of other mental disorders (Paper IV)
   c) neuropsychological performance in demented and non-demented 85-year-olds (Paper V).
BACKGROUND

INTRODUCTION

The number of elderly people is increasing in most western countries, especially in the oldest group (68). In 1985 the Swedish population aged 80 and above comprised 313,000 persons, and in 1990 370,000 (386). This figure is projected to increase to 448,000 in the year 2000 (386).

Old age, especially very old age, includes many stressors that might lead to an increased risk of mental disorders. These include: loss of spouse, loss of friends, loss of health in the elderly themselves and in their relatives, loss of social support, loss of job, financial losses, loss of independence, loss of intellectual capacity, loss of future dimension, and the approach of death (A161, 288).

However, life stressors might be better tolerated in old age because they are expected (31, A161). Old age may also have a positive dimension, with freedom of time, less stressors of work and less competition (A161). Elderly people have also been found to be more, or at least equally, satisfied with their life situation compared with younger people (31, A161).

Most authors have found that the majority of elderly persons with mental disorders are living in the community (A19, A183, 297). Their disorders are often not recognised by doctors (45, A183, 233, 286, 431) and hospital staff (A176, 286, 309), and they are seldom seen by a psychiatrist (309). The literature also demonstrates consistently low rates of help-seeking for emotional problems among the elderly (45, A195, 418, 419, 420, 431). Thus, many people with mental disorders, perhaps the majority, do not receive any formal psychiatric treatment (45, 222, 224, 233, 309, 420). Although the elderly constitute the great majority of people in institutions (69, A188), the hospitalisation rate for mental disorders declines with age (A159), and the cases seen by medical services may represent only a small fraction of those mentally ill (A172, A183, A188, 222, 244, 297, 328, 418, 419, 420). Therefore, to increase our understanding of mental disorders, it is necessary to study them in the general population (A183).

I. THE PREVALENCE OF MENTAL DISORDERS

The first epidemiological studies on mental disorders were based on indirect data collection through key informants or case records (for a review see A104). Later studies were based on
direct interviews with all subjects by a single psychiatrist who made a subjective diagnostic judgement, rarely supplemented with other data. After 1980 more systematic and refined diagnostic systems evolved and semistructured diagnostic interviews and rating examinations were introduced (A104). Many population studies, especially during recent years, have been concerned with the prevalence of mental disorders in old age (appendix 1-4). Comparisons of the results are, however, difficult to make owing to a number of methodological issues. These include questions related to the sample (size of sample, age composition, type of sample, screening procedures, representativeness), methods of collecting data (type of interviewer, content of examinations and interviews, criteria for rating symptoms and signs, or if complementary information has been used), diagnostic criteria (definition of cases, definition of severity) and, finally, which type of prevalence has been used (A183).

Prevalence may be measured as a point prevalence, related to a specific date, to the age of the subject or to the time of examination, or period prevalence, related to a month, a year, or a life-time. The longer time that is selected, the higher the prevalence will be. Too long a period may result in unreliable answers (86, A110). Prevalence is the product of the incidence and the average duration of the disorder (or survival time) (206, 381), and consequently depends on different survival for different diseases in different samples (93, 223, 259, 375).

Most earlier studies were based on representative samples of people over 65, in which the proportion and number of very old people was small. These studies are heavily weighted towards the younger part of the age strata, and will thus not reflect the situation among the very old. Enormous changes occur, however, in the 35 years between 65 and 100 (A159), and during recent years, many studies, especially on dementia, have also included substantial numbers of very old subjects (see appendix 1-4).

In the Scandinavian countries, the samples have generally been derived from the uniquely excellent census registers. Investigators in countries with less reliable census registers have to use other sources, e.g. the GPs lists, which are less reliable among the elderly (82, 263), or have had to make their own census lists. Another point is whether institutionalised subjects are included, which is most influential in the highest age-groups as more people are institutionalised in these groups (88, 259, 419).

As may be seen in appendix 1, the response rate varies between studies. Irrespective of the response rate, an analysis of the differences between responders and non-responders is necessary for the interpretation of the results in epidemiological studies. The effect of non-response is difficult to interpret and may differ between studies, countries and age-groups. Many studies report a higher non-response in higher age-groups, especially among the very old (45, 82, A180, 224, 232, 322, 328), where non-response due to death is difficult to avoid. The latter may influence the results in disorders with differential mortality. According to Jorm
et al. (205), refusal rates did not affect the prevalence of dementia in their review of 47 studies.

Interviews in epidemiological studies have been performed by lay interviewers, nurses or other health professionals, and different kinds of physicians, e.g. psychiatrists, GPs and internists. Employing physicians is more expensive and few studies have used this approach during recent years (362), except on screened cases in two-stage designs.

To increase reliability, standardisation of interviews and classifications have been introduced in recent studies (A104, 353). However, even standardised examinations are influenced by the experience and skill of the clinician (A104), the interview techniques adopted (275) and interactions with patients (275). Many different interview systems and formulations of items for symptoms and signs have been used, and several of them do not explicitly define their items, which may lead to low reliability.

Studies involving more detailed information collection in addition to personal interviews, e.g. supplementary information from an informant or medical and other official records, generally result in higher rates of disorders (A159, 205). Studies based on case records result in lower rates.

The cost and effort of making detailed investigations on total samples has led to the use of screening procedures, in which a more detailed examination is performed in subjects who are screened positive. Subjects screened negative may, however, have the disease (A127), which may lead to an underestimation of the real prevalence (A180). One method of determining the rate of false negatives is to examine a random sample of non-screened subjects (as in A141 and A180). A common screening instrument for dementia is the MMSE (A137), which is reported to be very satisfactory in identifying moderate and severe dementia at a cut-off point of 23/24 or 21/22 (76, 225) but poor in detecting mild dementia (76). Furthermore, even if the response rate is fairly high in each stage of the study, the cumulative response rate may be low. For example, in a study where the response rate is 70% in the first stage and 80% in the second stage, the cumulative response rate will be 0.7 x 0.8, that is 56% (205). Another problem is the time interval between screening and examination. If this time is too long, changes in the subjects might have occurred, which could influence the results.

The prevalence rate will depend on the criteria used for case definition, including the selection of symptoms and signs and their severity (26). A variety of diagnostic systems have been used, but even if the criteria are similar, the interpretations of them may differ between research groups (82, A127, 225, 383), as may the level at which cut-off points are chosen, which is an important reason for differences in prevalence between studies (83, A110, 207, 281, 353). Furthermore, criteria adopted for young persons may not be valid for the elderly.
Differences between the clinical setting and that in the general population include the fact that more people cluster around the diagnostic thresholds in the general population than in the clinical setting (29, 30, 82), and that psychiatric symptoms are common even in individuals who do not fulfill the criteria of a mental disorder (353). Furthermore, more subjects in the population have diseases of a mild degree (30, 82, 223, 353), while patient samples are generally in severer stages of the illness (263). Also, there are a number of subtypes and mild states that do not meet clinical criteria (29, A104). Finally, in community studies, there is active identification of cases, while in the hospital setting individuals seek treatment or are brought to attention by others (A127). Therefore, instruments developed and validated on patient samples might not have the same sensitivity (26, 350, 428) and specificity (350, 353, 428) in the community.

**Dementia**

Dementia is a syndrome of global cognitive decline that has many causes (A166, 219, 382). The dimensional rather than categorical character makes mild dementia sometimes difficult to separate from normal aging (26, 49, A184, 286, 300, 316, 366), especially in population studies (376). Fairly small differences in criteria may have a large effect on the prevalence rates (A127). Mowry & Burvill (300) found a variation in the prevalence of mild dementia ranging from 3 to 64% when different criteria were used on the same population. Different criteria also diagnosed different individuals. Furthermore, preconceptions about aging, or "the kind of bias that demands less of the very old", may lead to underestimation of the prevalence of dementia, especially among the very old (A159, 300). Another problem is that current diagnostic criteria underdiagnose frontal lobe dementia (A164) and subcortical dementia (A144).

The problems regarding cut-off points have led to a great variability in the rate of mild dementia reported in the community, and the figures vary tenfold, from 5 to 53% (A184). Concerning the prevalence of moderate and severe dementia, there are, however, rather unanimous results (68, A183, 205, see appendix 1). From the results of 47 prevalence studies conducted between 1945 and 1985, Jorm et al (205) found that the prevalence of moderate and severe dementia doubled every 5.1 years, reaching 11% in the age interval 80-84, 21% in the age interval 85-89 and 39% in the age interval 90-94. Most studies have included rather few individuals in the oldest age-groups, which makes the prevalence figures for these ages uncertain (205, 297). Recent studies, comprising substantial numbers in the oldest age-groups, confirm that the prevalence of dementia also increases in the most advanced ages (A141,
A180, A316). On the whole, there is no difference in the prevalence of dementia between different parts of the world, see appendix 1.

Although most clinical studies on dementia have been performed among the younger elderly, population studies show that the majority of demented subjects are to be found among those over 80 (A15, A138, A141, 221, 262). Between 66% and 69% of all demented subjects belong to this age-group (A15, 262).

Most studies report higher prevalences in males among younger old people (41, 93, A136, A172, A178, 241, 258, 259, 281, 310, 325, 341, 390, 419), and higher prevalences in women among the very old (A15, 93, A136, A141, A172, A178, A180, 241, 258, 259, 281, 341, 390, 419). Three studies, however, reported higher rates among women in all age-groups (75, 82, 262), and in two of them (75, 82) the female preponderance increased with age. Finally, some studies reported no sex difference (69, 221, 275, 316, 352). It has been suggested that more females have severe dementia (82, A112, 380), and accordingly prevalence studies of severe dementia generally have a female preponderance (A112, 328).

Differences between men and women in the prevalence of dementia may be explained by differences between the sexes regarding survival after the onset of dementia (A15, 241), institutionalisation rates (295) and incidence.

**Depressive disorders**

Some authors suggest that the clinical features of depression with onset late in life differ from the "typical" depression in younger persons (306), while others have stressed the similarities (303, 332). Elderly people have been suggested to be predisposed to depression due to age-related structural and biochemical changes (306, 332, 410) and the accumulation of psychological losses (A161). This notion might be supported by a world-wide report of disproportionately high rates of suicide in the elderly (A103). Several cross-sectional studies report, however, that the prevalence of depressive disorders decreases after 65 (27, 30, 32, 32, 83, 244, 255, 341, 419, 421, 422). There may, however, be an increase after the age of 75-80 (31, A154, 225, 231, 244, 259), at least for men (83), but data are limited in this age-group. Findings of a lower prevalence in the elderly may be related to exclusion of institutionalised subjects (32, 302), atypical features of depression in the elderly (32, 45, 234, 302), increased mortality in depression (32, 45, 302), a cohort effect with higher prevalences in later-born generations (31, 32, 45, 234, 302), the fact that the group above 65 has been treated as one entity, which might conceal an increase after 75, or it may actually reflect a lower incidence of depression after 70 (302).
Depressive symptoms are disproportionally more common than the clinical diagnosis of depression (30, 45), and although there might be a low prevalence of depressive syndromes in the elderly, the prevalence of depressive symptoms might increase with age (32, A140).

The prevalence of depressive disorders is given in appendix 2. Depression is generally more common in women (255, 341), also among the elderly (29, 82, 83, A158, 222, 232, 259, 262, 275, 309, 419). The female preponderance is most accentuated in middle life and decreases with age (A145, 207).

Schizophrenic and delusional disorders

DSM-III (7), but not DSM-III-R (8), ruled out schizophrenic cases with onset after 45 (85), which led to a conceptual bias and lower rates (A175), and a tendency to attribute schizophrenic symptoms to other causes (A175). It has been suggested that the low prevalence of late-onset schizophrenia may be due to underdiagnosis, reflecting the difficulty in identifying these cases in the general population (A175). The symptoms are similar to those of early onset (366) but personality is often more intact (A140, 333), as is premorbid adjustment (85, A140), compared with younger ages.

It has been estimated that 3% of all schizophrenics have onset after the age of 60 (85, A175). The first peak of admission for schizophrenia occurs between 25 and 34 years (A140), but there might be a second peak after the age of 75 (A183). The highest prevalence of schizophrenia in the population has been reported in the age-groups 25-44 (341), or 50-54 (255), with a decline thereafter (244, 255, 341). There might, however, be a leveling off between 65 and 74, and a rise after 75 (A154, A183). Few epidemiological studies have been concerned with psychotic disorders in old age, and the prevalences have generally been low (222, 244), as may be seen in appendix 3.

In younger age-groups more men are reported to have schizophrenia (A175), but at older ages there is a preponderance of women (85, A140, A175, 222, 309, 333).

Anxiety disorders

Very little has been written about the epidemiology of anxiety disorders in the elderly, see appendix 4. In the older literature, anxiety disorders were included among neurotic disorders, which makes comparisons difficult. It has been hypothesised that phobic avoidance may be a significant cause of houseboundness in the elderly (259). One indication of the importance of anxiety disorders in old age is the high consumption of anxiolytic drugs (259, 313, 379).

According to Lehtinen et al. (255), the prevalence of anxiety neurosis has a steep decline after 55, and according to Regier et al. (341, 342), DSM-III anxiety disorders have their lowest
rates after 65. Obsessional and phobic disorders appear to decrease with age (244, 342), and the latter were more common in younger elderly people than in the very old (259).

There are generally higher prevalences of anxiety in women (255, 341, 342, 419) although this was not confirmed by Lindesay et al (259). Phobic disorders are considered most common in women (255, 259, 419).

**Hypochondriasis**

Hypochondriasis is considered by many authors to be particularly common in the elderly (288), but this opinion has been contradicted by recent research (A16, 83).

**II. FUNCTIONAL MENTAL SYNDROMES IN DEMENTIA**

The patient described by Alzheimer (5) had delusional ideas and auditory hallucinations. For many years clinical studies on dementia were mainly concerned with the cognitive symptoms. During recent years, however, there has been an increased interest in other mental symptoms, which place a burden on caregivers (63, 64, 80, A135, 289, 434), affect the quality of life of the patients (434) and may be the critical factor in the decision whether or not to institutionalise a patient (80, 387, 434).

The concomitant occurrence of dementia and other mental disorders may have many explanations. First, mental disorders may cause or predispose to dementia (91, 434). Second, dementia may cause the mental syndrome (91). Third, both may be produced by the same common pathophysiology (91, 434). Fourth, the mental disorder may occur as a psychological response to the onset of cognitive impairment (91, A162). Fifth, clinical symptoms and diagnostic criteria of dementing illnesses overlap with those of depression (272, 289, 344), and type II schizophrenia (96), which can lead to the misdiagnosis of these mental disorders (91). Sixth, both dementia and other mental disorders are common in old age and may merely be co-incidental (434).

Pseudodementia is a dementia syndrome that is secondary to another mental disorder, mainly depression (330). Follow-up data indicate, however, that the majority of those with pseudodementia become permanently demented, sometimes after a period of recovery after treatment (243, 340). It is possible that a subclinical dementia becomes manifest during a concurrent depression (243). There may also be a risk of mistaking dementia for depression (340), as dementia simulating depression and depression combined with dementia is probably more common than pseudodementia (272, 329). Cognitive decline often accompanies schizophrenia (96) but opinions differ as to whether this is a true dementia or not (229, 252).
Other mental syndromes in demented subjects may be the result of neurochemical and neuroanatomical abnormalities (64, 91, A147, 289, 434, 440, 441) and may reflect clinically and pathologically distinct subgroups (64, 289, 434, 439, 441), with a specific pattern of cognitive decline (434), or specific location of the lesions (434).

The prevalence figures for other mental syndromes in demented subjects differ widely between studies, which may be attributable to differences in populations sampled (89, 272, 434), differences in duration and severity of dementia, different definitions of dementia disorders and mental syndromes (89, 272, 434), the methods of utilising and obtaining diagnostic information (89, 272), and whether the results are based on longitudinal or cross-sectional data (272), information from collateral sources (66, 272, 289, 344, 434), observation of behavioural signs (243) or reports from the patients. Many studies have not used formal criteria for their diagnoses. Furthermore, rating instruments may have unproven validity in demented populations (434). DSM-III-R has tightened the diagnostic boundaries for MDS in dementia (66, 272).

Non-cognitive mental symptoms are as a rule more common in early dementia (A178, 434), and Agbayewa (A1) reported that subjects with AD significantly more often had psychiatric illness earlier in life compared with controls (18% vs 4%).

**Depression:**

The association between depression and dementia has been noted since antiquity (276) and is the most discussed mental syndrome in dementia. Depressive symptoms are more common than depressive syndromes and have been reported in 0-87%, (58, 65, 91, A100, 394, 434), most studies giving figures of 40-50% (434). Depressive signs have been reported to be more common in MID than in AD (89). Reports from care-providers give higher rates: dysphoric symptoms were reported in 97% of demented subjects and other depressive symptoms in 33-93% (289).

Depression has been reported to occur in 0-86% of demented subjects (62, 65, 80, 89, 91, A111, A135, A157, 213, 234, 235, 243, 246, 249, 253, 272, 279, 289, 317, 328, 333, 343, 344, 345, 363, 368, 397), the majority of studies reporting rates between 20 and 30%. The study with zero per cent had depression as an exclusion criterion for entry to the study (235). The prevalence of DSM-III-R MDS in dementia was 4% according to a psychiatrist and 31% according to family (272). However, Burns et al., (65) found no patient with AD who satisfied these criteria.

Depressive states are believed to be especially common in MID (88, 89, 254). The figures reported for MID have varied between 25 and 70% (89, 91, A135, 254), and for AD between
0 and 80% (62, 65, 80, 89, A111, A135, 234, 235, 243, 246, 253, 328, 333, 345, 363, 368, 397), most studies having rates of 20-30%. The few studies comparing AD and MID have given conflicting results; Cummings et al. (89) had higher rates for MID than for AD, and Fischer et al. (A135) had no significant differences. In a study by Bucht et al. (59), 30% of MID patients, but only 5% of AD, had previous depression (59). At the time of examination, however, there was significantly more depression in the AD than in the MID group (59).

Few studies have used comparisons with normal controls (434); three studies (61, 246, 253) found increased prevalence of depression in demented subjects, three did not (62, 213, 235).

There appears to be less association between dementia and depression in community samples than in hospitals (30, 259, 317), although few studies have addressed this question. Kay et al (225), Lindesay et al (259) and O'Connor et al (317) did not find any strong correlation between dementia and depression in the community, but two other found a relationship (A158, A181).

Depression is generally more common in milder stages (31, 65, 89, A163, 289, 343, 344, 387) or earlier forms (80, A162, 276, 330) of dementia, which might be supported by the finding that AD-patients with depression had less ventricular enlargement on CT than other AD-patients (65). However, some studies found an association between depression in demented subjects and disability or difficulties with ADL (A158, 317) and cognitive impairment (A100, A157, 368). With regard to subtypes of dementia, depressed mood decreased with severity of AD, but there was no difference between different stages in MID (A135). The authors suggested that investigations of severely demented subjects may give the impression that depression is more common in MID (A135). Cooper et al. (80) found, however, that depression was not associated with declining MMSE in AD.

MDS may be a risk factor for mortality in demented subjects (439), but progression of dementia was the same (65, 344), or even slower (65), in demented subjects with depression.

Demented subjects with depression had significantly more degenerative findings and more NFTs in the locus ceruleus (A147, 439), substantia nigra (439) and basal nucleus of Meynert (A147). Depression in dementia has been suggested to result from decreased function of catecholaminergic (noradrenergic and dopaminergic) systems (A135, 276, 439, 440), but serotonergic dysfunction may also be important (91, 276, 440). On the other hand, the cholinergic defect in AD may have a protective effect against depression (89, 91, A135, 276), explaining the lower prevalence in severe dementia.

Although demented subjects with depression may benefit from antidepressants (A135, A157, 344), few are reported to be treated (65, A188, 344).
Psychosis

Psychotic symptoms, especially hallucinations, in demented subjects may express a psychotic syndrome, a misidentification syndrome or part of a delirium (434). Psychotic symptoms have been reported in between 20 and 58% of demented subjects (72, 80, A106, 234, 333, 363, 394, 434). In three longitudinal studies on AD, half of the subjects developed at least one psychotic symptom during their illness (72, A106, 363).

Psychotic symptoms have been associated with increasing severity of dementia (80, A100, A106, 363), with a more rapid cognitive decline (A106, 270, 299, 363, 434), and with increasing age (80), but have not been associated with an increased mortality (A106, 363).

Delusions

Delusions, most often persecutory (A100, 434), have been reported in 4-73% of demented subjects (21, 81, A100, A106, A111, 246, 270, 289, 345, 394, 396, 397, 434). Two studies claimed that paranoid ideation was more common in VaD compared with AD (A178, 289), two found no difference (89, 21). Paranoia was significantly more common in AD patients than in controls in one study (246). In AD, rates have varied between 4 and 57% (21, 64, 81, 89, A100, A106, A111, A178, 246, 345, 396, 397), and in VaD between 16 and 50% (21, 64, 89, A178).

There are conflicting results whether delusions are early or late manifestations of dementia (89). Delusions have been reported to be more common in less cognitively impaired subjects (89, 333), in more cognitively impaired subjects (81, A100, 299, 434), or to have no relation to severity (64, 89, A162, 289), but faster progression was predicted by the presence of delusions in two studies (270, 299).

Hallucinations

Hallucinations have been reported in 0-49% of demented subjects (20, 66, 81, 89, A100, A106, A111, 246, 270, 289, 299, 345, 394, 396, 397, 434), visual in 0-26% (20, 66, 89, A100, 270, 345, 434) and auditory in 1-13% (66, 89, A100, 270, 434). Visual hallucinations have been reported in 0-26% of AD (20, 66, 89, A100, 270, 299, 345), and in 20-27% of MID patients (20, 89), and auditory hallucinations in 1-10% of AD (66, 89, A100, 270, 299) and 7% of MID patients (89). Few studies have compared AD and MID. One study found a weak association with MID (89), another found no difference (20). Hallucinations may be difficult to separate from misidentification syndromes, which have been reported in 30% of AD patients (66). Hallucinations correlated to severity of dementia in two studies (81, 289) - the
finding was, however, not corroborated by three other (66, A100, 299) - and faster progression in two studies (270, 299).

Structural changes reported in the brains of schizophrenic patients (96) are similar to those reported in patients with Alzheimer's disease (403), including enlargement of lateral ventricles (96), reduced temporal lobe size (96), hippocampal changes (96), reduced cell numbers in the limbic system (96) and progressive cerebral atrophy (286). In demented patients, those with a psychotic syndrome have been reported to have increased densities of SPs and NFTs (441) and reduced levels of serotonin (441). Delusions correlated with basal ganglia calcification (64) and higher ventricular brain ratio on CT (64). AD patients with hallucinations had a greater reduction in serotonin binding sites in the cortex (427).

**Anxiety**

Few authors have studied anxiety in dementia in a systematic way. One population study found no association (259). Others have noted that anxiety comes early in dementia (A162, A165, 286, 425). Reported prevalences have been 12% in AD (345) and 52% in MID (254), while Swearer et al (394) reported that 63% of demented patients exhibited anxiety, which was not related to severity or type of dementia.

**III. TYPES OF DEMENTIA**

Dementia syndromes occur with more than 60 diseases (A166, 219), the most common being Alzheimer's disease and vascular dementias (219).

**Alzheimer's disease**

The histolopathological diagnosis of Alzheimer's disease is based on the findings of excessive amounts of senile plaques (SPs) and neurofibrillary tangles (NFTs) (53, 227, 403). The typical clinical picture is a dementia syndrome with an insidious onset and a slowly progressive course, which is reflected by the NINCDS-ADRDA criteria (285). Since the mid-70s early-onset and late-onset AD have been treated as one entity. There are, however, indications that they may constitute two distinct entities (367), with less temporo-parietal symptoms (34, A165), more confusion (34), more WMLs (33, 257) and more non-focal cerebrovascular symptoms (A114) in the late-onset form.

**Vascular dementia:**

Until about 30 years ago, dementia was considered a result of chronic ischaemia secondary to atherosclerosis of cerebral arteries or "hardening of the arteries" (9, A151, A170, A171, 292).
In 1974, Hachinski et al (A167) introduced the term multi-infarct dementia, which shifted the emphasis on aetiology from the brain to the heart and extracranial arteries (A171, 251). Thereafter the occurrence of multiple small or large infarcts came to be considered almost the only basis of VaD (416). In the late 1970s the scientific emphasis in the study of dementias swung from vascular to primary degenerative disorders and Alzheimer's disease (28, A151, 357), and vascular dementia came to be regarded as less common (A170). Current scientific discoveries are pushing the pendulum back towards greater interest in circulatory mechanisms (28). During the last few years the term "vascular dementia" has been introduced, but it is still used almost synonymously with the concept of multi-infarct dementia (372, A126). However, MID is not the only type of vascular dementia (97, A126, A139, A170, 200, 266, 315, 321, 360, 372). Other forms include WMLs with dementia, hereditary cerebral haemorrhage with amyloidosis, granular cortical atrophy, hypertensive encephalopathy, cerebral amyloid angiopathy, cerebral vasculitis and haemodynamic dementia (for reviews see A123, 360, 414). In many cases there is a combination of changes (A126, 301). The two most common types are probably multi-infarct dementia and dementia related to white-matter lesions of the brain.

**Multi-infarct dementia**

MID is a dementia syndrome evolving in connection with multiple small or large brain infarcts (A126, A167), often too small individually to produce a major clinical incident (A167, 395). Most cerebral infarcts are due to thrombo-embolism from extracranial arteries and the heart (A167). The clinical picture involves sudden onset (A118, 264, 412), stepwise deterioration (A118), a fluctuating course (A118, 412), history of stroke (A118, 264, 412), focal neurological symptoms and signs (A118, 264, 412) and hypertension (412).

**Haemodynamic dementia**

Haemodynamic dementia (or hypoperfusion dementia) refers to a dementia with onset in connection with an episode of severe systemic hypotension (391). All patients with a clinical diagnosis of haemodynamic dementia had, however, a picture of MID at autopsy (A124). Treating the haemodynamic type as a separate entity may therefore be questionable (A124).

**Mixed dementias**

The common coincidence of AD and VaD is becoming increasingly recognised (35, A126, A170, 200, 227, 278, 292, 395, 401), and this may even be the most common form of dementia (A171, 372). Neither alone may be sufficient to cause dementia, but together they may (28, A124, A170, 278, 292, 395, 423). On a clinical basis, it is, however, difficult to differentiate mixed dementia from MID (A167, 292, 411).
**Hachinski Ischemic score**

Many studies, both those from evaluation units and population studies, have used the Hachinski ischaemic score (IS) for the diagnosis of multi-infarct dementia. The ischaemic score was outlined by Hachinski et al in 1975 (A168) and was derived from the description of atherotrombotic dementia in the Mayer-Gross textbook Clinical Psychiatry (283). In Hachinski et al's study (A168), patients fell clearly into two groups with regard to the results of CBF. A score of 7 and above indicated MID, 4 or less AD. Some later studies have used a score of 5 or 6 as an indication of mixed AD/VaD (e.g. A141, 354). The IS has been criticised for only predicting that a patient has had a stroke or infarcts and not that these caused the dementia (56, 265, 315, 372). Moreover, there is a lack of more detailed definitions of the score items and their severity, leaving room for individual interpretations (A126, 366), as well as a lack of statements about the temporal connection between the items and development of cognitive symptoms (A126) and a lack of internal consistency. For example, it is unclear whether patients with score 8 have less vascular changes than those with 18 (A126). Finally, results of measurement by means of symptom scales cannot easily be translated into clinically useful diagnostic criteria (419), and many disorders can produce similar scores (84). The score has later been modified by some authors (for a review see A123).

**Other causes of dementia**

Besides AD and VaD, many other disorders, some of which are potentially treatable, may result in a dementia syndrome (A166, 219, 248, 250, 286, 408). In studies from dementia evaluation units, 5-45% of cases have been found to be potentially reversible, most studies reporting 10-20% (92, A143, 248, 279, 346). Recent follow-up data indicate, however, that most cases of so-called reversible dementia do not revert to normality (92, A143, A192, 248, 249, 286) and continue to show a progressive decline (92, 248). The diseases might have caused irreversible neuronal loss (330, 366) or potentiated the symptoms of a pre-existing dementia (366). However, it is still important to treat such conditions as they may aggravate the dementia (A159, 249, 286, 366). The high incidence of concomitant physical disorders in the elderly makes it difficult to determine whether they caused, contributed to, or were merely co-incidental with dementia (A10, A159, A187, 219, 248, 249, 366). If the definition of AD or VaD requires that all other potential causes of dementia should be excluded, it will eliminate all cases in which some other condition coexists, which is not appropriate in the oldest age-groups (A159).

**Proportions of different types of dementia**

The aetiological diagnosis of dementia is difficult to make on the symptomatology only (227), because of the similarities in clinical pictures between different forms of dementia (278, 372),
and there is still no biological marker for the diagnosis of AD or VaD (A126). Therefore, auxiliary investigations are necessary (209, 250, 286, 330, 366, 408), including careful history-taking, neurological, psychiatric and physical examinations, interview of a close informant, CT-scans of the head, a chest X-ray, biochemical screening including vitamin B₁₂ level, a thyroid function test (219, 250, 429) and, if suggested by other findings, examination of cerebrospinal fluid (219). These investigations have not been available in community-based studies, which makes the aetiological differentiation of dementia difficult in this type of study (A185, 209, 263, 298, 355). Furthermore, the expense and difficulty in performing such investigations in the general population has caused several authors to state that such studies are not likely to be performed in the immediate future (A185, 263, 298, 329, 355).

So far, only the MID-type of VaD has been investigated in population studies, see appendix 5. Generally, AD is the most common diagnosis in western countries (A127, A141, 216, 355), although high proportions of MID have also been reported (A136). Some studies report a very low proportion of MID (A15, A127, 240, 263, 316, 328).

The prevalences of both AD and MID increase with age. Most studies find, however, that the prevalence of AD rises more sharply with age than that of MID (49, A178, A188, 240, 316, 355, 442). Therefore, most studies report that the relative proportion of MID decreases with increasing age, while that of AD increases (49, 51, A178, 275, 316, 355, 390). This also holds true for Japan, where MID was the most common dementia before the age of 80, after which AD became most common (A178). The decreasing proportion of MID with age may be due to the higher mortality in MID (49). Finally, it has been suggested that the steady decline in stroke incidence, and better treatment of hypertension, may lead to a declining incidence of MID (315).

AD is generally reported to be more common in females (A10, 68, A138, 205, 216, 220, 221, 222, 241, 275, 297, 305, 316, 354, 380, 390), although some studies report the opposite (41, 328), and others report no sex difference (A141). AD is sometimes reported to be particularly common in females in the oldest age-groups (A15). MID, on the other hand, is more common in males (A15, A138, A178, 205, 221, 222, 275, 297, 316, 354, 355, 380, 390), although there are reports of the opposite (258, 305), and of no sex difference (A141). There are indications of a female preponderance in the highest age-groups (305, 355), and that the sex difference in MID rates diminishes in the oldest age-groups (A10, 316).

Although the prevalence of dementia is similar in most parts of the world, there are differences regarding the type of dementia. MID is reported to be more common in Finland, the former Soviet Union and in Asian countries (205), including Japan (A178, A188, 214, 221, 380) and China (258), than in western Europe and the USA, where AD is generally reported to be the most common type of dementia (205). The differences might be due to
differences in diagnostic criteria, differences in the rate of cerebrovascular disorders, or constitutional or environmental factors (A178, A188).
Secondary or potentially treatable forms of dementia are generally rare in population studies (49, 84, A136, 263, 316), and the proportion seems to decrease with age (A141). They are mostly mild (49, A178) and more common in men (93, 305).

The proportions of different types of dementia have also been studied in autopsy studies and in evaluation units. However, such studies may have selection bias (A138, 315, 324), and changes might occur between examination and autopsy (A187). With these biases in mind, AD, or "senile dementia", is most often reported to be the commonest type in both autopsy studies and evaluation units (Appendix 5). Studies from evaluation units pertain to patients having reached the units (A183), which is influenced by the clinical picture of the disorder, including severity (A127, 419), an atypical picture (32, A127), or disturbed behaviour (214, 387), referral practices (A187, 248, 286, 374) and the extent of evaluations performed by primary care physicians (374). Patients with an obvious cause for their dementia will not be referred for further evaluations (A151, A187, A192, 248, 279), which may be the reason for the very low proportions of vascular dementia and rather high proportions of secondary dementias generally reported from such units (A151, 249, 250, 286). AD is, however, generally the most common type also in these studies (286), see appendix 5.

IV. WHITE MATTER LESIONS

After the advent of CT, interest has increased in vascular dementia with white-matter lesions in the brain (54, A170, 308, 357, 372). First described by Durand-Fardel in 1854 (A108, A179), followed by Binswanger in 1894 (25), and by Alzheimer in 1898 (6), fewer than 50 autopsied cases were described in the world literature up to 1980 (A14, A169, 357). Since 1980, when WMLs became possible to discern on brain imaging, they have been reported in hundreds of patients (278, 308, 357). This "epidemic" caused some authors to question the validity of WMLs as a diagnostic entity (A169, A170), and they have been claimed to be overemphasised (278).

However, before the advent of CT, the level of interest among pathologists in WM disorders was low and the WM was not routinely evaluated in detail in most patients (A152, 308, 372), which is necessary as the lesions are difficult to detect without whole brain sections (54, 357), and myelin staining (A152, 357, 372). The true incidence may therefore be much higher than formerly believed (A14, A152, A186, A196, 228, 334, 357, 404), and it may even be the most common form of VaD (301). The increased interest is reflected by the fact that more than 230 autopsied cases with the typical histological picture have been described after 1980 (e.g. A14, 37, 54, 94, A132, A149, A150, A152, A186, A194, A196, 228, 242, 271, 334, 347, 404, 438). However, no epidemiological study of WMLs has so far been performed and the prevalences reported are mainly based on patient samples.
Neuropathology

The pathological description includes marked or diffuse demyelination and moderate loss of axons with astrogliosis and incomplete infarction in subcortical structures of both hemispheres and arteriosclerotic changes with hyalinisation or fibrosis and thickening of the vessel walls and narrowing of the lumina of the small penetrating arteries and arterioles in the WM (A14, 24, 24, 60, 70, 98, A130, A132, A149, A150, A152, A194, A196, 200, 228, 271, 318, 334, 347, 364, 404, 438), often accompanied by a reduction of oligodendrocytes (A14, 24, 54). The cortex is generally well preserved (A14, 24, 98, A114, A130, A152, A196, 267, 347, 404, 438), as are the subcortical U fibres (A14, A17, 24, 54, 60, 98, A130, A132, A149, A152, A194, 267, 318, 334, 347, 364, 404) and corpus callosum (395), probably due to a different blood supply. The changes are often associated with lacunar infarcts (A14, A17, 24, 60, 70, 98, A149, A194, 200, 318, 364, 404). In 15 studies or case reports on the clinicopathological correlations of subjects with WMLs on CT, the histopathological picture described above has been reported in 53 out of 55 autopsied cases (A14, 37, A149, A150, A152, A160, 211, 228, 242, 267, 334, 347, 364, 438), and Janota et al (A197) described myelin pallor in 11 out of 12 patients with WMLs on CT but related it to CAA.

Many terms have been used for a similar pathological entity. Alzheimer (1902) (6), coined the term Binswanger's disease, which has been used extensively (e.g. A17, 24, 37, 98, A196, 271, 308, 318, 357). Other terms include subcortical arteriosclerotic encephalopathy (e.g. 99, A152, 228, 267, 318), arteriolosclerotic leucoencephalopathy (A132), leucoencephalopathy (A150), senile leucoencephalopathy (360), subcortical encephalomalacia (A13), or selective incomplete white-matter infarction (54). For the entity seen on CT or MRI, the above-mentioned terms have been used as well as white-matter low attenuation (A125, 407, 438), white-matter lesions (WMLs) (33), periventricular WM lucencies (347), and leuko-araiosis (2, A169, 236). In the following presentation, the term WMLs is used to describe the findings on CT, MRI and autopsy.

WMLs have been described in both clinical and autopsied cases of Alzheimer's disease (54, 94, A101, A132, A150, A152, 242, 271, 347, 398, 399, 403), and they seem to be more common in late than in early AD (33, 54) and often occur independently of the gray matter processes in AD (33, 54, 94, A116, 398). AD may be difficult to differentiate from the dementia associated with WMLs as the clinical picture is similar. De la Monte (94), in a study on non-demented subjects with extensive AD lesions, found prominent and selective atrophy in the WM, with no atrophy in cortical or subcortical GM areas despite numerous NFTs and SPs, and suggested that WM degeneration precedes and causes the cortical atrophy in AD.

Risk factors
WMLs have been associated with vascular diseases, especially hypertension (A14, 60, 70, A126, A132, A139, A142, A150, A152, A160, A170, A193, A194, A196, 228, 267, 271, 287, 357, 372, 404, 407, 438), although there are studies reporting no association with hypertension (33, 36, 54, A150, 321) or blood pressure levels (A101, A125, A193, 347, 415). It may be that these subjects had previous high blood pressure levels which were normalised at the time of examination (A142, 271, 404).

Pathogenesis

The main hypothesis regarding the cause of WMLs is that longstanding hypertension causes lipohyalinosis and thickening of the vessel walls with narrowing of the lumen of the small perforating arteries and arterioles which nourish the deep WM (A142, A196, 267, 357). Episodes of hypotension (A142, A171, A196, 404), related to for example aging, drugs or cardiac failure, may lead to hypoperfusion and hypoxia-ischaemia, leading to loss of myelin in the WM (A14, 54, 70, 98, A114, A121, A132, A142, A152, A194, 228, 267, 271, 357, 404). The deep WM has few collaterals (A14, A121, A152, 357), which makes it more vulnerable to ischaemia than the cortex when a penetrating vessel occludes (A169). Furthermore, myelin is probably more vulnerable to ischaemia than axons (A115, A170). In the early stages, remyelination may occur if the underlying cause of hypoperfusion is eliminated (A115). The lesions may also remain stable after a single episode of hypoperfusion (A116). It has been suggested that the arterial changes are due to exposure of vessel walls to increased pressure over time (271). The greater the pressure and/or lifespan, the more likely are these changes to be present (357). Others consider, however, that no convincing proof of this theory exists (70, 372). Alternative hypotheses include late effects of cerebral oedema (A14, 60, A130, 267, 301, 337), destructive enzymes or other poisons which pass through hyalinosis-damaged vessel walls (416), or dysfunction of the endothelial carrier systems leading to deficient supply of nutrients (416).

The dementia associated with WMLs is probably caused by subcortical-cortical (A114, A119, A170, A194, 357, 372, 395, 416) or cortico-cortical (94) disconnection. Delayed central conduction time has been found in patients with WMLs, which might support this opinion (217).

Clinical picture

WMLs have been associated with a spectrum of clinical pictures ranging from no memory disturbances (70, 98, A132, 287) to dementia (37, A130, A132, A152, A160, A194, 228, 267, 268, 271, 357, 364, 404, 407, 438). As a rule, the dementia has an insidious onset (A142, 267, 357) and a slowly progressive course (A14, 24, 70, A142, A144, 228, 267, 318, 357, 372),
which makes it difficult to distinguish from AD (24, A196). In the initial stage, there are often transient and fleeting attacks of focal neurological deficits (A14, 24, 70, 267, 357), with a subacute accumulation of focal deficits (70, A144, 267, 357).

The dementia is generally of a subcortical type (33, 99, 99, A121, A144, 228, 228, 357, 357, 416), with symptoms of a frontal lobe syndrome (37, A152, A160, A194, 357, 416). The clinical picture includes bilateral (A144, 357) or unilateral pyramidal tract signs (A14, 70, A144, A194, 267, 357, 388), with bilateral (A160, 267) or unilateral paresis (A14, 37, 70, A144, A152, A160, A160, A170, 228, 228, 267, 267, 318, 321, 347, 438), and hemi- or motoranaesthesia (70, A152, A160, 228, 267, 318), pseudobulbar palsy (A17, 37, 70, A144, A152, A160, 212, 267, 357, 404, 438), extrapyramidal signs (A14, A17, 267, 357, 404) with psychomotor retardation (37, 60, 70, A194, 357), urinary incontinence (A14, A17, A17, 37, A142, A144, A152, A194, 228, 357, 364, 404), gait dysfunction (A14, A17, A17, 37, 60, A142, A144, A150, A152, A160, A194, 228, 267, 268, 357, 357, 364, 407), apathy (A14, 24, 37, A144, 357, 357), loss of drive (A14, 37, 37, A144, A194, 267, 357) and emotional blunting (37, A144, A160).

Prevalence of WMLs in normal and demented people

The prevalence of WMLs on CT has not been studied in population samples. Differences in prevalence between studies may be due to methodological differences, including cohort differences, the age composition of the population sampled, the type of sample, definition of "normality" (236), exclusion criteria used (236), definitions of WMLs (A101, 236), definitions of dementia and its subtypes (A101), the severity and duration of dementia (A101), the sensitivity of the scanner (A101), the experience of the radiologist (A101) or the improved recognition of WMLs during recent years (A101).

Having these methodological differences in mind, studies on consecutive CT-scans have given prevalences between 0.1 and 8%, mostly between 1 and 3% (A102, 228, 267, 287, 334, 407, 438). Studies on non-demented controls have given rates of 0% in subjects below the age of 50 (95, A150, A152, 236, 437), 22% in normal volunteers of mean age 54 years (236), and between 7 and 42% in elderly controls, mostly with mean ages around 70 (95, A150, A193, A199, 268, 347, 388, 389). Two studies gave age-specific figures. Goto et al. (A152) had 3% in the age strata 50-59 years, 12% in those 60-69 years, 29% in 70-79-year-olds, and 38% in those aged 80-89 years. George et al. (A150) had 7% in 55-69-year-olds, and 24% in 70-85-year-olds.

In studies on demented populations, the prevalences have generally been higher, between 19 and 97% (2, 95, A101, A118, A119, A125, A150, A193, 268, 347, 388). The results depend on the age of the subjects and the type of dementia studied. In Alzheimer's disease, the rates have varied between 19 and 62%, most studies having rates of about 30% (2, 33, 95, A101,
A119, A125, A150, A193, 236, 268, 321, 347, 388, 415). Studies comparing early and late-onset AD have generally found higher rates of WMLs in late-onset AD. The figures given have been 18% vs 35% (A150), 12% vs 80% (415), 2% vs 46% (A119) and 24% vs 76% (33). In MID the rates are generally reported to be higher, between 46 and 97%, most studies having rates between 55 and 75% (2, A118, A119, A199, 236, 268, 321, 415). In MID, there seems to be no difference between age-groups (A119). In mixed dementia the prevalences have varied between 19 and 75% (A118, A119, A193, 321, 388).

With regard to the impact of the degree of dementia, the reports have been contradictory. Some studies report an increased prevalence of WMLs with more severe dementia (A101, A119, A125, 204) while others do not (33, A119, A120, 321, 415). The severity or extent of WMLs on CT was not related to the occurrence of dementia (271, 287, 347), the severity of dementia (A132, A150), or MMSE scores (2) in some studies, but has been correlated with mental deterioration or dementia in other studies (A146, 347). Erkinjuntti et al. (A125) reported faster progression in demented subjects with WMLs than in those without. The duration of dementia has not been associated with WMLs (A114, A125, 415).

MRI studies have generally reported substantially higher rates of WMLs than CT-studies. In non-demented subjects, lesions in subcortical and deep WM increased from 11% in the fourth decade to 83% in subjects over 70 (A129).

The figures from autopsy studies on unselected samples have shown white-matter lesions in 4% of all autopsied brains at age 60 and over (404), but 7% in those with signs of cerebrovascular diseases (404). Ferrer et al. (A132) had 52% in subjects with a mean age of 62 years. These lesions were rare in the fourth and fifth decade, and increased thereafter to reach a prevalence of 100% at the age of 80 (A132). In demented subjects, the rates of WMLs in those with AD have varied between 50 and 90% (54, 94, A132, 347), the bulk of studies having rates around 60%. One study reported somewhat higher rates in late-onset AD; 55% vs 68% (A114). An autopsy study on MID had a rate of 100% (A132).

In summary, a constant finding is that WMLs become more common with increasing age in both demented and non-demented subjects (A14, A17, 33, A101, A119, A120, A125, A132, A150, A152, A193, 228, 236, 268, 357, 388, 389, 407, 415, 437). Most studies do not report any sex differences (e.g. A14, A125, A193, 204, 388, 415).

**WMLs and other mental disorders**

It has been suggested that the first manifestation of WMLs may be psychiatric (290). In subjects with WMLs, there have been reports of changes in mood (A14, 24, 70, A144, A194, 267, 357) and psychotic symptoms (A14, A144, 404). Most studies reporting an association
between functional mental disorders and WMLs have been performed with MRI. WMLs on MRI have been reported in subjects with bipolar disorders (A105, A107, 331, 385, 393), in unipolar disorders (A105), in major depression (245, 335), in elderly depressives referred for ECT (78), in subjects with geriatric depression (A191), in late-onset schizophrenia (50) and in late-life psychosis (V94). On CT WM attenuation has been associated with MDS (323), and in demented patients with late-life psychosis (290).

In one study on bipolar disorders, the WMLs on MRI did not resolve when the disorder did (A107), while lithium normalised T<sub>1</sub>-values of WM in bipolar patients in another study (338). It has been hypothesised that increased T<sub>1</sub>-values may reflect dysregulation of intracerebral ionic and water distribution in depression (A105), or an increase in intracellular free water (331), which indirectly reflects an altered membrane structure (331).

**WMLs and neuropsychological performance**

The influence of WMLs on cognitive function has been debated. Comparisons between subjects with and without WMLs on CT have revealed that subjects with WMLs had lower performance on global measures of cognitive function in non-demented subjects (389), a picture of subcortical dementia, with psychomotor slowness, in unselected samples (99, A160), but two studies on demented subjects did not find any significant differences (269, 388). Most studies on non-demented subjects have not found any differences in neuropsychological performance between subjects with and without WMLs on MRI, when age is taken into consideration (4, A190, 226, 339, 405), exceptions being Ylikoski et al (435) and Junqué et al. (212), showing increased slowness of mental processes, and Boone et al. (44), showing deficiencies in frontal lobe skills in subjects with WMLs. Kobari (237) demonstrated a correlation between cognitive scores and WMLs on CT, but not WMLs on MRI.

In demented subjects, Almqvist et al (4) found an association between WMLs on MRI and lower performance in visuoconstruction, attention and finger-motor speed, while Harrell et al. (A174) found worser neuropsychological performance in AD patients with severe WMLs..
METHODS

SUBJECTS

The present study is part of the gerontological and geriatric population studies in Gothenburg, Sweden (H70), which started in 1971 (311, 325, 348, 392).

All 85-year-olds born between 1 July 1901 and 30 June 1902 and registered for census purposes in Gothenburg, Sweden, were invited to take part in a health survey (n=1502). Both people living in the community and those in institutions were included. A systematic subsample, consisting of every second person from the census register, was selected for a psychiatric examination (n=826). The basis for selection was the following procedure: all persons in the census register were consecutively (after date of birth) given a number from 1-5 or 11-15. Those with number 1, 2, 11, 12 or 14 were selected for the psychiatric examinations.

The study was performed in three steps. First, a nurse made a visit to the subject's home, then the subject was invited for an examination at the geriatric outpatient clinic of Vasa Hospital, and finally the psychiatric examination was performed in the subject's home.

Fortythree subjects died before the psychiatric examination, leaving an effective sample of 783 subjects. Fourteen (1.8%) had moved or could not be traced, 229 (29.2%) refused all investigations, 17 (2.2%) took part only in the nurse interview, and 29 (3.7%) refused further examinations after the visit to the geriatric outpatient clinic. Four hundred and ninetyfour subjects (63.1%) (143 men and 351 women) were finally examined by the psychiatrist. Non-participants (excluding those who died before the examination) and participants were compared with regard to sex, marital status, mortality rate up to the age of 88 years, institutionalisation and registration as a psychiatric outpatient or inpatient in Gothenburg. No differences were found with regard to these factors (table 1). The mean age at the actual examination was 85.5 years (range 85 years 3 months-86 years 1 month).
TABLE 1 COMPARISONS BETWEEN PARTICIPANTS AND NON-PARTICIPANTS IN THE STUDY OF 85-YEAR-OLDS (%)

<table>
<thead>
<tr>
<th></th>
<th>Participants</th>
<th>Non-participants</th>
<th>n.s.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>29</td>
<td>25</td>
<td>n.s.</td>
</tr>
<tr>
<td>Females</td>
<td>71</td>
<td>75</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
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<tr>
<td>Never married</td>
<td>15</td>
<td>16</td>
<td>n.s.</td>
</tr>
<tr>
<td>Married</td>
<td>23</td>
<td>21</td>
<td>n.s.</td>
</tr>
<tr>
<td>Divorced</td>
<td>8</td>
<td>6</td>
<td>n.s.</td>
</tr>
<tr>
<td>Widowed</td>
<td>54</td>
<td>56</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Institutionalisation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>10</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Psychiatric registration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>13</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death before 88</td>
<td>25</td>
<td>28</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

n.s. = non significant

METHODS

Examinations

General examination

During the home call a registered nurse interviewed the subjects on their social and living conditions and their need of social and medical care. The probands were also thoroughly interviewed on their drug consumption. The prescribed and actually taken dose was registered,
and classified according to the Anatomical Therapeutic Chemical (ATC) classification system recommended by the WHO (247, 312).

The examination at the geriatric outpatient clinic has been described previously (348, 392) and included a physical examination by a geriatrician, neuropsychological examination by a psychologist, laboratory tests including ECG, chest X-ray and an extensive biochemical evaluation including blood tests such as erythrocyte sedimentation rate, haemoglobin, red and white blood cell counts, thrombocytes, hematocrit, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, blood folates, vitamin B12, iron, total iron binding capacity, ferritin, glucose, potassium, sodium, chloride, calcium and phosphorous, proteins including albumin, immunglobulin G and haptoglobin, urea, urates, creatinine kinase, LD, gamma-GT, phosphates, cholesterol, triglycerides, free fatty acids, phospholipids, kidney, liver and thyroid function tests, urine tests for protein, glucose, erythrocytes and leucocytes and a test for haemoglobin in faeces.

**Psychiatric examination**

All psychiatric examinations were performed by the author in the subject's home or at institutions where they were living. The mean length of the examination was 83 minutes (range 20-191 minutes). The examination was semi-structured and comprised questions in the following order: parents' age when the proband was born, circumstances during early life, life events during the last five years (e.g. death of spouse or child), present health of spouse, history of epileptic seizures, stroke or TIA, alcohol consumption, previous mental disorders, diseases in first-degree relatives (history of dementia, Down's syndrome, mental disorders or lymphoproliferative diseases), thoughts about death and suicide, psychiatric symptoms during the month preceeding the interview, current use of psychotropic drugs, sexual activity and sleep.

Psychiatric symptoms and signs were rated in accordance with the Comprehensive Psychopathological Rating Scale (CPRS) (443). Signs common in dementia (i.e. personality changes and motor symptoms) and tests of mental functioning were rated; recent and remote memory, orientation for time, place, person and situation, knowledge of general information, motor/face apraxia, agraphia, alexia, acalculia, constructional apraxia, ideational apraxia, ability to understand proverbs, ability to follow commands, finger agnosia, right-left disorientation, abstract and concrete estimation, judgement, naming ability, language abnormalities, motor abnormalities, Klüver-Bücy syndrome, reactions during testing, confabulation and decreased inhibition. The Mini Mental State Examination (137), the short version of the Blessed test (218), the Gottfries-Bråne-Steen Scale (GBS) (153), and a global rating of mental health were also performed. After the interview, the subjects were given three personality inventories to fill in at home and return by mail: the Eysenck Personality Inventory
(128), the Marke-Nyman Temperament Scale (314) and the Cesarec-Marke Personality Schedule (71).

**Interview of a close informant**

After the examination, the proband was asked for permission to interview a close informant. For demented subjects a close informant was sought in other ways. An interview with a close informant was performed by the author by telephone in 451 cases (91%). The proband refused or did not have a close informant in 40 cases (8%) and the close informant refused in 3 cases (1%). The mean length of the interview was for informants of non-demented subjects 28 minutes (range 9-65 minutes) and for informants of demented subjects 52 minutes (range 15-95 minutes). The interview was semi-structured and comprised questions about changes in behaviour and intellectual function: global changes in personality, memory, orientation, difficulties in finding way in familiar surroundings, intellectual ability, language, speech, motivation, decreased inhibition, feelings for others, suspiciousness and paranoid ideas, delusions, hallucinations, sleep disturbance, confusion, depression, lacrmosity, hypochondriasis, anxiety and worries, irritability, aggressive behaviour, performances in activities of daily living, incontinence, gait and motor difficulties, epileptic seizures, myoclonia and insight in disease. Questions were asked about when and how the symptoms first appeared and, if any, when they disappeared. Information about background factors like diseases in first-degree relatives of the examinee (history of dementia, Down's syndrome, other mental disorder or lymphoproliferative diseases), age of mother and father at the birth of the subject, history of stroke, head trauma, exposure to solvents, infectious diseases, abuse of alcohol, deficiency states, low pressure hydrocephalus and/or brain tumours was collected. For demented subjects, questions about age and symptoms at onset and course were also asked.

The mean interval between the examination at the outpatient clinic and the psychiatric examination was 2 weeks (range 0-16 weeks) and between psychiatric examination and interview of a close informant 5 months (range 0-11 months).

**Neuropsychological examination**

The neuropsychological examination was performed by a psychologist without knowledge of the results from the psychiatric and CT examinations. The following psychometric tests were administered:
- Synonyms, measuring verbal ability (SRB1). The maximum score is 30.
- Figure Classification, measuring inductive reasoning (SRB2). The maximum score is 30.
- Block Design, measuring spatial ability (SRB3). The maximum score is 42.
- Identical forms, measuring perceptual speed (Ps-IF). The maximum score is 60.
- Thurstone Picture Memory Test measuring secondary memory. The maximum score is 28. The pictures were enlarged in order to minimise problems owing to visual deficiencies in the subjects.
- Digit Span, measuring primary memory. The maximum score is 9 in the forward and 8 in the backward subtest.

The above tests, except Digit Span, are from Dureman & Sälde (109). Block Design and Digit Span are also parts of the WAIS (417). The use of these tests in the H 70 study has been described elsewhere (18).

The following brief neuropsychological tests were also administered:
- The Clock Test, which is similar to the widely used Draw-a-Clock procedure (I), but with the addition of having subjects set (II) and tell (III) the time on a large wooden clock. The maximum score is 15.
- The Coin Test, which is designed as a sorting task, using familiar stimuli to test concept formation and basic arithmetic abilities. The maximum score is 8.
- The MIR Memory Test, in which subjects are shown a three-dimensional model of an apartment and asked to place 10 real-life objects in different rooms. Tests of free recall and recognition are administered to determine the subject's ability to remember the objects and their locations. The maximum score on each sub-task is 10.
- A Prose Recall Test, similar to the prose passages in the Wechsler Memory Test. The maximum score is 16.

The four tests above have been described by Johansson & Zarit (203).
- The Ten-Word memory test is a traditional supra-span list learning task, containing two ten-word lists, one of animals (I) and the other of cloths (II), corresponding to Buschke & Fuld (67). The maximum score in each list is 10.

CT-scan examinations

All demented (n=147) and a systematic subsample of 269 non-demented subjects were invited to undergo computed tomography (CT-scan) of the head. Subjects who had been examined in a longitudinal study from age 70 to 85 did not have a CT-scan examination, if it was not part of a dementia evaluation. These subjects had numbers 1 and 2. Thus, non-demented subjects with numbers 11, 12, and 14 were selected for the CT-scan examinations. One-hundred and three (70.1%) demented and 136 (50.6%) non-demented accepted. Three CT-scans were excluded from the study in paper IV and V for technical reasons. Within the demented and non-demented groups, there were no differences between participants and non-participants with regard to sex, marital status, mental disorders, institutionalisation, three-year mortality and cardiovascular disorders. All CT-scans were examined by two experienced neuroradiologists. One hundred and thirtythree were performed on a Philips Tomoscan 310 and 106 on a General Electric 8800.
Other examinations

The first 165 participants were invited to undergo lumbar puncture. Sixty-nine (31 demented and 38 non-demented subjects) accepted.

Medical records from psychiatric and geriatric institutions and outpatient departments in Gothenburg were examined by the author.

Diagnostic procedures

Dementia

First, a diagnosis of dementia was made from the psychiatric examination and the close informant interview separately using DSM-III-R criteria (8) (Table 2 and 3). Each symptom had to attain a level causing significant difficulties in social life. A final diagnosis was made from the combined information using four steps. The final diagnosis and its severity was registered according to DSM-III-R (8). The duration had to be at least 6 months.

Other mental disorders

The diagnoses of other mental disorders were made as close as possible to the DSM-III-R criteria (8). The symptoms had to be present during the month preceding the interview. It was not possible to use the duration criteria of DSM-III-R in this study because of lack of information. Therefore, schizophrenic and schizophreniform disorders were treated as one entity, and dysthymia as a form of mild depression (225).

Other mental syndromes in demented subjects

To be able to study mental syndromes in demented subjects, the exclusion criteria of DSM-III-R were omitted in paper III. This procedure has been used by others to study the co-occurrence of mental syndromes (46). As this is not the exact definition of the DSM-III-R criteria, the term syndrome has been used instead of disorder. A subject was not allowed to have more than one depressive syndrome and one psychotic syndrome in this paper. The diagnoses were based on symptoms noted during the last month. Comparisons were not made for the diagnoses depression NOS or psychosis NOS, which here correspond to cases with depressive and psychotic features which did not fulfil the symptom criteria for major depression (MDS), dysthymia, delusional syndrome or schizophreniform syndrome. These diagnoses were, however, included in the overall groups of depressive syndromes and psychotic syndromes in Paper III.
TABLE 2 ITEMS FROM THE PSYCHIATRIC EXAMINATION USED IN THE DIAGNOSIS OF DEMENTIA (DSM-III-R)

<table>
<thead>
<tr>
<th>Item</th>
<th>(n)</th>
<th>rs</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Impairment in at least one of:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-term memory</td>
<td>49</td>
<td>0.95</td>
</tr>
<tr>
<td>Long-term memory last ten years</td>
<td>23</td>
<td>0.97</td>
</tr>
<tr>
<td>Long-term memory more than ten years</td>
<td>50</td>
<td>0.93</td>
</tr>
<tr>
<td>Past and present prime ministers</td>
<td>22</td>
<td>1.00</td>
</tr>
<tr>
<td>B. Impairment in at least one of:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstract thinking (proverbs)</td>
<td>21</td>
<td>1.00</td>
</tr>
<tr>
<td>Anomia</td>
<td>21</td>
<td>1.00</td>
</tr>
<tr>
<td>Expressive aphasia</td>
<td>24</td>
<td>0.89</td>
</tr>
<tr>
<td>Impressive aphasia</td>
<td>23</td>
<td>1.00</td>
</tr>
<tr>
<td>Language ability</td>
<td>23</td>
<td>0.83</td>
</tr>
<tr>
<td>Understanding spoken language</td>
<td>22</td>
<td>0.89</td>
</tr>
<tr>
<td>Difficulties finding words</td>
<td>22</td>
<td>0.82</td>
</tr>
<tr>
<td>Motor apraxia</td>
<td>23</td>
<td>1.00</td>
</tr>
<tr>
<td>Following command</td>
<td>22</td>
<td>0.85</td>
</tr>
<tr>
<td>Ideational apraxia</td>
<td>21</td>
<td>1.00</td>
</tr>
<tr>
<td>Fingeragnosia</td>
<td>23</td>
<td>1.00</td>
</tr>
<tr>
<td>Constructional difficulties</td>
<td>21</td>
<td>0.99</td>
</tr>
<tr>
<td>Aggressive behaviour</td>
<td>50</td>
<td>0.79</td>
</tr>
<tr>
<td>Decreased inhibition</td>
<td>24</td>
<td>1.00</td>
</tr>
<tr>
<td>Loss of personal property</td>
<td>23</td>
<td>0.79</td>
</tr>
<tr>
<td>Emotional bluntness</td>
<td>52</td>
<td>0.76</td>
</tr>
</tbody>
</table>

(n)= number of subjects participating in the co-ratings
rs=Spearman's rank correlation coefficient of interrater reliability for each item
Table 3 ITEMS FROM THE CLOSE INFORMANT INTERVIEW USED IN THE DIAGNOSIS OF DEMENTIA (DSM-III-R)

<table>
<thead>
<tr>
<th>A diagnosis of dementia from the close informant interview required A and B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Impairment in at least one of:</strong></td>
</tr>
<tr>
<td>Short-term memory</td>
</tr>
<tr>
<td>Long-term memory</td>
</tr>
<tr>
<td><strong>B. Impairment in at least one of:</strong></td>
</tr>
<tr>
<td>Getting lost in familiar surroundings</td>
</tr>
<tr>
<td>Language ability</td>
</tr>
<tr>
<td>Difficulty finding words</td>
</tr>
<tr>
<td>Apraxia</td>
</tr>
<tr>
<td>Global personality change</td>
</tr>
<tr>
<td>Losing interests</td>
</tr>
<tr>
<td>Decreased initiative</td>
</tr>
<tr>
<td>Emotional bluntness</td>
</tr>
<tr>
<td>Decreased inhibition</td>
</tr>
<tr>
<td>Irritability</td>
</tr>
</tbody>
</table>

Types of dementia

Subjects with dementia were classified into aetiological subgroups:

*Alzheimer's disease* was diagnosed according to NINCDS-ADRDA-criteria (285).

*Vascular dementia* (multi-infarct dementia, probable vascular dementia/mixed dementia and hypoperfusion dementia) and other causes were diagnosed according to criteria proposed by Erkinjuntti (124).

*Muti-infarct dementia* was diagnosed when there was one or more infarcts on CT and/or a temporal connection (within one year) between the first symptoms of dementia and a history of acute focal neurological symptoms and signs (restricted to definite symptoms or signs, e.g. acute hemiparesis, acute motor aphasia), *probable vascular dementia/mixed dementia* when there was a history of acute focal neurological symptoms and signs without any clear temporal
connection with the evolution of dementia (more than one year), and hypoperfusion dementia when there was a temporal connection between the onset of dementia and a history of severe systemic hypotension.

*Other causes* were diagnosed when dementia evolved in temporal association with a neurological, mental or systemic disorder of sufficient degree to produce dementia.

All criteria are close to those of DSM-III-R (8).

*The Hachinski Ischemic Score* (168), which is an often-used check-list containing clinical features known to be common in multi-infarct dementia, was used, but only for comparison with other studies, and not for the final aetiological diagnosis.

Diseases which could contribute to dementia but were not considered to be the primary cause were recorded as proposed by Roth (366).

The aetiological diagnoses and the Hachinski Ischemic Score were based on information gathered from all examinations and from case records.

**White matter lesions**

WMLs were defined as periventricular or subcortical areas of decreased attenuation below that expected for normal white matter. The changes were always diffusely distributed within the white matter. Decreased attenuation was subjectively rated as no, mild, moderate, or severe in relation to the attenuation of normal white matter. Location was registered as frontal (mainly around the frontal horns around the lateral ventricles) or occipital (mainly around the occipital horns around the lateral ventricles).

**Inter-observer reliability**

Inter-observer reliability regarding psychiatric symptoms and signs was studied by simultaneous independent co-rating of 52 individuals on items common to all previous psychiatric examinations in the longitudinal studies and of 25 individuals on items which were new for the present study. The subjects were chosen from the ongoing studies and from inpatients at a psychiatric clinic. Inter-observer reliability was estimated with the Spearman rank correlation coefficient. Inter-rater correlation coefficients for symptoms and signs pertaining to the diagnosis of dementia are given in table 2. The correlation was satisfactory. Inter-observer reliability was not studied for the informant interview.
Inter-observer reliability regarding causes of dementia was studied on all demented cases with kappa statistics (77). For the three main diagnostic categories, the observed agreement was 94.6%, Kappa 0.90 (p<0.001).

Inter-observer reliability regarding the occurrence and severity of WMLs was studied in 50 subjects using Kappa statistics (77). Observed agreement was 84.0%, Kappa 0.75 (p<0.001).

**Statistical methods**

Differences in proportions were tested for significance with Fisher's exact test (79). Associations with severity of dementia were tested with Pitman's permutation test (79). Bayes' theorem (79) was used to calculate the probability of the occurrence of dementia in different degrees of decreased attenuation of WMLs in paper IV. In paper III and V, the results were pooled with regard to sex, using a method suggested by Mantel (277). A stepwise logistic regression analysis in a personal computer (370), using the 5% level of significance, was performed to study the contribution of WMLs and infarcts on CT for the occurrence of dementia. The two-tailed level of significance was used in all analyses.

Informed consent was obtained from all subjects and/or their relatives. The study was approved by the Ethics Committee for Medical Research of the University of Gothenburg.
RESULTS

I. THE PREVALENCE OF MENTAL DISORDERS (Papers I and II)

a) The prevalence of mental disorders is shown in table 4.

<table>
<thead>
<tr>
<th>Type of mental disorder</th>
<th>Percentage of subjects</th>
<th>Men (N=143)</th>
<th>Women (N=351)</th>
<th>All (N=494)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia</td>
<td></td>
<td>27</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td>Any other mental disorder</td>
<td></td>
<td>21</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>Depressive disorders</td>
<td></td>
<td>12</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Psychotic disorders</td>
<td></td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td></td>
<td>6</td>
<td>13*</td>
<td>11</td>
</tr>
<tr>
<td>Hypochondriasis</td>
<td></td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Sex difference; *=p<0.05 N=number of subjects
One subject may have more than one diagnosis.

Of all subjects, 8% had mild, 10% moderate and 11% severe dementia. The results were similar for men and women. The most common diagnoses, other than dementia, were depressive disorders (13%). All five subjects with hypochondriasis also had a depressive disorder.

There were no significant differences in the prevalences between the sexes except for the group of anxiety disorders and its subgroups generalized anxiety disorder/panic disorder and phobic disorder, which were significantly more common in women.
b) The use of psychotropic drugs is shown in table 5 (paper II).

**TABLE 5 USE OF PSYCHOTROPIC DRUGS IN 85-YEAR-OLDS**

<table>
<thead>
<tr>
<th>Type of drug</th>
<th>Percentage of users</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men (N=143)</td>
<td>Women (N=351)</td>
<td>All subjects (N=494)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiolytic-sedatives</td>
<td>26</td>
<td>38*</td>
<td>34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>8</td>
<td>17**</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuroleptics</td>
<td>3</td>
<td>7</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any psychotropic drug</td>
<td>30</td>
<td>48***</td>
<td>43</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sex difference: *=p<0.05, **=p<0.01, ***=p<0.001

As may be seen in the table 5, almost half of the women and one-third of the men used a psychotropic drug. The most commonly used drugs were anxiolytics-sedatives. Women used significantly more psychotropic drugs than men, except for neuroleptics. The rate of psychotropic drug use was significantly higher in institutionalised (74%) than in non-institutionalised (37%) subjects (p<0.001). The difference pertained mainly to the use of anxiolytics and antidepressants.
c) The use of different psychotropic drugs in relation to type of mental disorder is shown in table 6 (Paper II).

**Table 6 The use of psychotropic drugs in different mental disorders in 85-year-olds**

<table>
<thead>
<tr>
<th>Type of mental disorder</th>
<th>Anxiolytic sedatives (%)</th>
<th>Antidepressants (%)</th>
<th>Neuroleptics (%)</th>
<th>Any psychotropic drug (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No mental disorder</td>
<td>26</td>
<td>3</td>
<td>4</td>
<td>29</td>
</tr>
<tr>
<td>Dementia</td>
<td>38*</td>
<td>31***</td>
<td>6</td>
<td>57***</td>
</tr>
<tr>
<td>Depressive disorders</td>
<td>52***</td>
<td>19***</td>
<td>10</td>
<td>60***</td>
</tr>
<tr>
<td>Psychotic disorders</td>
<td>30</td>
<td>9</td>
<td>9</td>
<td>35</td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>50</td>
<td>12*</td>
<td>10</td>
<td>52**</td>
</tr>
</tbody>
</table>

Comparison with subjects without any mental disorder:

*p<0.05, **p<0.01, ***p<0.001

As may be seen, only one-fifth of those depressed received antidepressants and only one-tenth of those with psychotic disorders received neuroleptics. Those depressed received mainly anxiolytic-sedatives. The condition with the largest consumption of antidepressants was dementia. The use of antidepressants increased with severity of dementia; 3% of subjects with no mental disorder, 15% of those with mild dementia, 22% of those with moderate dementia (p<0.01, compared to non-demented subjects) and 53% of those with severe dementia (p<0.001, compared to non-demented subjects) used antidepressants.

Sex differences in the use of psychotropic drugs is shown in table 7: Women used several psychotropic drugs significantly more often than did men and this occurred in several conditions.
TABLE 7 SIGNIFICANT SEX DIFFERENCES IN THE USE OF PSYCHOTROPIC DRUGS IN DIFFERENT MENTAL DISORDERS

<table>
<thead>
<tr>
<th>Mental disorder</th>
<th>Type of drug</th>
<th>Men</th>
<th>Women</th>
<th>Differences between the sexes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any mental disorder(^1)</td>
<td>Anxiolytic-sedatives</td>
<td>27</td>
<td>51</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Any mental disorder(^1)</td>
<td>Any psychotropic drug</td>
<td>33</td>
<td>57</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Depressive disorders</td>
<td>Anxiolytic-sedatives</td>
<td>24</td>
<td>62</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Depressive disorders</td>
<td>Any psychotropic drug</td>
<td>29</td>
<td>71</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>No mental disorder</td>
<td>Any psychotropic drug</td>
<td>19</td>
<td>34</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

1=any mental disorder except dementia

---

d) Institutionalisation (Paper I and II):

Forty-eight per cent (48\%) of demented subjects, 3\% of subjects with other mental disorders and 1\% of subjects with no psychiatric diagnosis were institutionalised at nursing homes or geriatric or psychiatric long-stay wards.

The rate of institutionalisation in relation to severity of dementia was: mild dementia 10\%, moderate dementia 37\% and severe dementia 88\%.

The rate of institutionalisation in relation to type of dementia was: Alzheimer's disease 38\%, vascular dementia 62\% and other dementias 29\%. Differences compared to non-demented, p<0.001 and Alzheimer's disease vs vascular dementia, p<0.01.
II. FUNCTIONAL MENTAL SYNDROMES IN DEMENTIA (Paper III)

The prevalence of functional mental disorders in relation to dementia and its severity is shown in table 8.

<table>
<thead>
<tr>
<th>Mental syndrome</th>
<th>No dementia (N=347)</th>
<th>Mild (N=41)</th>
<th>Moderate (N=51)</th>
<th>Severe (N=55)</th>
<th>Any dementia (N=147)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Depressive syndromes</td>
<td>20</td>
<td>34*</td>
<td>26</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>Psychotic syndromes</td>
<td>7</td>
<td>12</td>
<td>12</td>
<td>18**</td>
<td>14**</td>
</tr>
<tr>
<td>Anxiety syndromes</td>
<td>23</td>
<td>29</td>
<td>24</td>
<td>18</td>
<td>23</td>
</tr>
</tbody>
</table>

Difference against non-demented: *=p<0.05, **=p<0.01, N= number of subjects

Psychotic syndromes and its subgroup schizophreniform syndrome were significantly more common in demented subjects than in non-demented. Phobia was less common.

Psychotic syndromes and its subgroup schizophreniform syndrome were more common in severe dementia, while depressive syndromes were more common in mild dementia, compared with non-demented subjects.
Psychotic syndromes (19% vs 7%, p<0.01) and its subgroup schizophreniform syndrome (13% vs 1%, p<0.001) were more common in subjects with Alzheimer's disease than in non-demented subjects.

III. TYPES OF DEMENTIA (Paper I)

The proportions of different types of dementia (%) are shown in table 9.

**Table 9 Proportions of types of dementia in 85-year-olds**

<table>
<thead>
<tr>
<th>Types of dementia</th>
<th>Percentage distribution</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men (N=39)</td>
<td>Women (N=108)</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Alzheimer's disease</td>
<td>44</td>
<td>44</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>33</td>
<td>52</td>
</tr>
<tr>
<td>Other dementias</td>
<td>23</td>
<td>5**</td>
</tr>
</tbody>
</table>

Sex difference: **=p<0.01

The proportion of Alzheimer's disease was the same for men and women, multi-infarct dementia (21% vs 40%, p<0.05), mixed dementia (0% vs 11%, p<0.05) and multi-infarct/mixed dementia (21% vs 51%, p<0.01) were significantly more common in women, and dementia due to other causes was more common in men than in women (p=0.002).

Other concomitant disorders which could cause dementia but were not considered to be the main cause were: B12 deficiency (n=9), alcohol abuse (n=8), temporal arteritis (n=3), severe cardiovascular disease (n=3), depression (n=3), chronic schizophrenia (n=2), hypothyroidism (n=2), normal pressure hydrocephalus (n=1), syphilis (n=1), infectious disease (n=1), multiple diseases (n=1), hyperthyroidism (n=1), hypercalcaemia (n=1), borrelia infection (n=1) and epilepsy (n=1).
The proportion of vascular dementia differed if different criteria and samples were used, see table 10.

<table>
<thead>
<tr>
<th>TABLE 10 PROPORTION OF SUBJECTS WITH VASCULAR DEMENTIA AMONG SUBJECTS WITH DEMENTIA USING DIFFERENT CRITERIA AND SAMPLES IN 85-YEAR-OLDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
</tr>
<tr>
<td>Vascular dementia in the present study *</td>
</tr>
<tr>
<td>Multi-infarct dementia in the present study *</td>
</tr>
<tr>
<td>Diagnosis made without knowledge of the CT-scan</td>
</tr>
<tr>
<td>Focal findings and a positive CT scan #</td>
</tr>
<tr>
<td>Hachinski Ischemic Score 5 or more</td>
</tr>
<tr>
<td>Hachinski Ischemic Score 7 or more</td>
</tr>
<tr>
<td>If only community-dwelling subjects were studied *</td>
</tr>
<tr>
<td>If only institutionalized subjects were studied *</td>
</tr>
<tr>
<td>If only subjects undergoing a CT scan were studied *</td>
</tr>
</tbody>
</table>

* = Diagnosis with the criteria used in this study
# = Only incuding subjects performing a CT

CT-scanning in demented subjects showed postoperative subdural haematoma in one case and indicated presence of normal pressure hydrocephalus in four cases, of which the diagnosis was confirmed in one. The prevalence of infarcts on CT was 28% in demented and 13% in non-demented subjects (p<0.01)

Analysis of cerebrospinal fluid was performed in 31 demented subjects; none of these analyses revealed pathological changes indicating a secondary cause of dementia.

The three-year mortality was 23% for non-demented subjects, 42%, for Alzheimer's disease (p<0.01), 67% for vascular dementia (p<0.001) and 57% for other causes (p<0.01). p=difference from non-demented. Alzheimer's disease vs vascular dementia, p<0.01.
IV. WHITE MATTER LESIONS (Papers IV and V)

a) WMLs in relation to dementia (Paper IV)

WMLs in relation to dementia are shown in table 11

**TABLE 11. PRESENCE OF WHITE MATTER LESIONS (WMLs) IN RELATION TO SEVERITY OF DEMENTIA IN 85-YEAR OLDS**

<table>
<thead>
<tr>
<th>Severity of dementia</th>
<th>Proportion of subjects with WMLs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No dementia</td>
<td>34</td>
</tr>
<tr>
<td>Mild</td>
<td>59*</td>
</tr>
<tr>
<td>Moderate</td>
<td>73***</td>
</tr>
<tr>
<td>Severe</td>
<td>72***</td>
</tr>
<tr>
<td>Any</td>
<td>69***</td>
</tr>
</tbody>
</table>

Comparison with subjects without dementia:
* = p<0.05, *** = p<0.001

All grades of severity and all types of dementia were associated with significantly higher prevalence of WMLs, but the occurrence of WMLs was unaffected by sex and did not differ significantly between different severities or types of dementia.

Using Baye's theorem (79), the risk of dementia in subjects without WMLs was 16%, in subjects with mildly decreased attenuation 35% (p<0.01), in subjects with moderatly
decreased attenuation 57% (p<0.001) and in subjects with severely decreased attenuation 75% (p<0.01; p= difference against non-demented). Difference between mild and moderately dementia; p<0.05. There was, however, no correlation between degree of decreased attenuation and severity of dementia.

A stepwise logistic regression analysis was performed to study the contribution of WMLs and infarcts on CT to the occurrence of dementia. The procedure showed that both WMLs (p<0.001) and infarcts on CT (p<0.05) independently contributed to the occurrence of dementia.

**b) WMLs in relation to functional mental disorders (Paper IV)**

The prevalence of WMLs was not increased in non-demented subjects with other mental disorders. Demented subjects with concomitant other mental syndrome did not differ from demented subjects without such disorders with regard to the prevalence of WMLs.

**c) Neuropsychological performance in relation to WMLs (Paper V)**

Significant differences in neuropsychological performance between subjects with and without WMLs in one demented and one non-demented group are shown in table 12.

<table>
<thead>
<tr>
<th>Type of test</th>
<th>Among non-demented subjects</th>
<th>Among demented subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No WMLs (means)</td>
<td>WMLs (means)</td>
</tr>
<tr>
<td>Block design</td>
<td>12.6</td>
<td>9.0 **</td>
</tr>
<tr>
<td>Perceptual Speed</td>
<td>14.4</td>
<td>11.9 *</td>
</tr>
<tr>
<td>Picture Memory</td>
<td>19.5</td>
<td>16.9 *</td>
</tr>
<tr>
<td>Clock Test I</td>
<td>4.2</td>
<td>3.8 *</td>
</tr>
<tr>
<td>Clock Test II</td>
<td>5.2</td>
<td>4.5 *</td>
</tr>
<tr>
<td>MIR Memory Test</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Ten Word Memory I</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
</tbody>
</table>
Differences between subjects with and without WMLs: *\( p<0.05 \), **\( p<0.01 \)
WMLs= white matter lesions. n.s. = non-significant
DISCUSSION

I. THE PREVALENCE OF MENTAL DISORDERS

Comments on the results:

Dementia

This study showed a prevalence of dementia at 85 years of nearly 30%, which is in accordance with Magnuson (275). Some recent population studies (75, 295, 316) have reported a lower prevalence of dementia in the oldest age-groups than earlier studies did, which has resulted in speculation as to whether it could be due to overestimation in earlier studies, a real decline in prevalence or the use of instruments with low sensitivity in the later studies (75, 84). The prevalence of moderate and severe dementia (21%) in the present study is in line with most earlier and contemporary population studies (Appendix 1). No differences were found with regard to sex, which is in accordance with Magnusson (275) and O'Connor (316). Although the prevalence of dementia after 65 is generally the same for men and women (205), most studies show a higher prevalence in women in the oldest age-groups (75, 83, 178, 262, 295, 354, 390).

Other mental disorders

Paper II showed that other mental disorders than dementia are also common at high ages. Comparison with other studies is difficult due to methodological differences, see appendix 1-4. The prevalence of depressive disorders (13%) in this study was close to that in most other studies (see appendix 2). Only a few reports have given prevalences of psychotic disorders in the oldest age-groups (see appendix 3). The present study gave a somewhat higher rate (5%) than other studies. There are also few studies dealing with the prevalence of anxiety disorders (see appendix 5).

Anxiety disorders and the subgroups generalised anxiety disorder/panic disorder and phobic disorder showed a female preponderance. The lack of sex difference regarding depression in this study is in agreement with the notion of diminishing sex differences for depression with increasing age (207). In older age-groups, women have been suggested to have higher rates of schizophrenic and psychotic disorders than men (175) but this study does not support this opinion. However, the number of subjects with psychotic disorders was small.
The use of psychotropic drugs and rate of institutionalisation

Paper II confirms the high rate of psychotropic drug use in the elderly. The rate of 43% for the use of any psychotropic drug in this 85-year-old population is similar to the 48% found by Bowling (45) in subjects 85 years and older, but higher than the rates from studies concerned mainly with younger groups of elderly subjects (133, 247, 296, 320). Despite the high rate of prescription of psychotropic drugs, a substantial proportion of those persons with mental disorders did not receive any specific treatment for their disorders. Only one-fifth of those with depressive disorders received antidepressant therapy, and only one-tenth of those with psychotic disorders received neuroleptics. This may be due to underdiagnosis of mental disorders or to hesitation to use these drugs in elderly populations because of higher rates of side effects (313). A low rate of treatment for mental disorders has been reported in other western countries as well, both in the past (41, 222, 309, 431) and more recently (45, 82, 195, 233, 262, 420). Many subjects had symptoms of a mild degree. However, even mild cases, like those found in the community, might have considerable impairment of functioning and well-being (422), and may respond well to pharmacological or psychological treatment (32, 383).

Another interesting finding was the high rate of prescription of psychotropic drugs, especially antidepressants, in cases of dementia. This applied especially to institutionalised subjects, where more than three-quarters received a psychotropic drug and more than half an antidepressant. This may be due to a desire to treat and detect pseudodementia, or concomitant depression in demented subjects. Although demented subjects with depression may benefit from antidepressant medication (344), they are also more sensitive to the side effects of the drugs.

Studies from nursing homes and geriatric and psychiatric long-term wards show that the majority of the patients in these institutions are demented (176, 219, 369). The present study further emphasises the importance of dementia for institutionalisation in old age as only 1% of subjects with no psychiatric diagnosis were institutionalised in nursing homes and geriatric or psychiatric long-stay wards at the time of examination, compared with 10% of subjects with mild dementia, 37% of those with moderate dementia and 88% of those with severe dementia.

Comments on methods

Sample

This investigation pertains to a large sample of very old people. The sample also included institutionalised subjects, which is important since institutionalisation is common in this age-
group (88, 259, 419). The response rate was somewhat lower than in earlier examinations of the longitudinally followed samples from this project (311, 325, 348, 392). The high age of the population may be one explanation, in agreement with earlier reports (45, 82, 180, 225, 232, 291, 322, 328). Although there is a possibility that there may be a difference in response rate between subjects with and without mental syndromes, the finding that there were no differences between responders and non-responders with regard to sex, marital status, use of mental health services, institutionalisation and mortality up to the age of 88 years indicates that the sample investigated was representative of the total group of 85-year-olds (table 1).

Collection of data

All subjects in this study were examined by an experienced psychiatrist, in contrast to many studies during recent years in which lay interviewers were used. A psychiatrist may be better qualified for the observation of behaviour (362), making it possible to use the observational criteria in DSM-III-R (8), has more experience in disclosing symptoms, may better appreciate the non-verbal ingredients in an interview (362) and is more able to evaluate the history. The participants may also be more willing to report psychiatric symptoms to a psychiatrist than to a lay interviewer (353), which may lead to higher morbidity rates (380). On the other hand, psychiatrists may rate mental illness "down" in relation to their experience of more severe illness (83, 86, 225, 322).

The use of operationalised criteria and well-defined formulations of items for symptoms and signs increased the reliability. As expected, the inter-rater reliability was higher for reported than for observed items.

The requirement that the diagnosis of dementia should be confirmed both by the clinical examination and by the informant interview takes the premorbid ability into account. This decreases the likelihood of including persons with a transient intellectual decline, life-long level of low cognitive function or low education (208). Furthermore, the use of an informant interview facilitated identification of persons of high intelligence and/or high education who concealed their mild dementia, by revealing a decline from a previously very high level. Key informants are also necessary for the use of DSM-III-R criteria of personality change and clouding of consciousness (225). However, family members may deny negative changes in the subjects (328, 408) or discount changes in the very elderly as being normal for age (208, 442), and they include many different people with varying backgrounds and observational skill (275, 328). Finally, the subjects may differ with regard to the availability of family or friends (127). It has been stated that the use of informant interviews consumes too much resources and would not be appropriate for large community surveys (184, 225). However, the experience from this study shows that they are possible to perform and that they are important in the diagnosis of mild dementia.
Diagnostic criteria

The diagnoses were based on DSM-III-R (8) symptom criteria during the last month, without taking other duration criteria into consideration, due to incomplete information. This might have resulted in an overestimation, especially of dysthymic disorder, which here corresponds to a form of mild depression (225). The same approach has been used by another group (225). On the other hand, the duration criteria of DSM-III-R are somewhat arbitrary and may have a low reliability due to recall biases in community studies, and it has been claimed that questions about symptoms during the month before examination are more reliable (86, 110).

Symptoms of depression may overlap with physical diseases or normal ageing (225), thus giving artificially high rates. On the other hand, if depressive symptoms are falsely thought to be due to physical diseases or normal aging, the rate of depression may be underestimated.

The use of psychotropic drugs was not taken into consideration in the diagnostic procedures. It is probable that some mental disorders were not manifested because of the treatment, thus leading to underestimation of the number of persons with mental disorders.

II. FUNCTIONAL MENTAL SYNDROMES IN DEMENTIA

Comments on the results

A systematic comparison between demented and non-demented subjects regarding mental syndromes in representative population samples has not been performed previously. The prevalence of psychotic syndromes in demented subjects was similar to or lower than that found in patient samples (64, 66, 80, 89, 363, 434), but significantly higher in subjects with dementia and its subgroup Alzheimer's disease than in non-demented subjects. Furthermore, the finding from other studies that psychotic syndromes become more common with increasing severity of dementia (80, 289, 363) was corroborated. It may be hypothesised that some of the brain changes seen in Alzheimer's disease (403), which have also been reported in some forms of schizophrenia (96), may predispose to psychotic symptoms.

The concomitant occurrence of depression and dementia has received much attention (91, 276, 344) and is one of the items in the Hachinski scale (168). The prevalence of depression in demented subjects in the present study (25%) was fairly similar to the 10-20% found in patient samples (65, 91, 157, 344, 363, 368, 434) but not significantly different from that in non-demented subjects (20%). A lack of association between dementia and depression in community studies has been noted by others (259, 317). However, depression was most
common in mild dementia, which is in line with some other studies (65, 80, 135, 163, 276, 289, 344, 434).

Anxiety in dementia has not been studied as extensively as psychosis and depression. In this study, the prevalence of anxiety syndromes did not differ significantly between non-demented and demented subjects.

**Comments on the methods**

In the diagnosis of other mental syndromes in demented subjects, we used the DSM-III-R (8) symptom criteria as we wanted to use well-defined operationalised criteria. However, DSM-III-R excludes organic causes, including dementia, in some disorders. It was therefore necessary to omit these exclusion criteria. This procedure has been used by others to study the simultaneous occurrence of mental syndromes (46). As this is not the exact definition of the DSM-III-R criteria, the term syndrome has been used instead of disorder.

Some factors in this study might have diminished the possibility of finding differences in the prevalence of mental syndromes between demented and non-demented subjects. First, the figures pertained to one-month prevalence. Various mental syndromes may appear in different phases of the dementia process (363). If so, a longer observation period might have resulted in higher rates of other mental syndromes in demented subjects. Second, interviews with caregivers generally give higher rates of psychopathology in demented subjects than a single clinical examination (272, 289), which was the routine in this study. Third, it is possible that demented subjects, due to diminished memory and cognitive capacity, fail to describe all their symptoms adequately and thus do not exhibit all the criteria necessary to establish a syndrome diagnosis (91, 368, 434). This may be most evident in severe stages of dementia (89). Fourth, the use of psychotropic drugs was not taken into consideration when diagnosing concomitant mental syndromes. It is possible that some subjects had a mental syndrome that was not manifested because of the treatment, thus leading to underestimation of the prevalence of mental syndromes. On the other hand, some of the symptom criteria for dementia overlap with those of depressive syndromes and the negative symptoms of schizophreniform syndrome. This may artificially inflate the rates of these syndromes in demented subjects.

Although we did find an association between psychotic syndromes and dementia, and between depression and mild dementia, the results do not allow any aetiological conclusions. The findings may reflect either secondary changes of dementia disorders or an increased risk of dementia in subjects with previous and long-standing mental syndromes. The cross-sectional design limits the possibilities of distinguishing between these two possibilities. However, two recent reports from our group regarding cases of dementia developing between the ages of 70 and 79 did not show an increased rate of mental syndromes before the onset of dementia (326, 327).
Furthermore, reports from key informants in the present study indicate that the majority of concomitant mental syndromes developed after the onset of dementia (and during recent years in non-demented subjects). However, key informants may have a poor knowledge of earlier mental syndromes in the subjects.

Finally, the findings may be related to the high age of the sample, and the clinical expression may vary with age. Thus, the results may be different in younger age-groups. Indeed, Cooper et al (80) found that hallucinations and delusions increased with age in demented subjects. Consequently, the occurrence of mental syndromes in demented subjects should be studied in representative samples of younger elderly subjects too.

III. TYPES OF DEMENTIA

Comments on the results

The proportion of vascular dementia was higher than in most population studies from European and North-American studies (205) and higher than reported from autopsy studies and from evaluation units, despite the fact that Sweden has one of the lowest stroke mortality rates in the world (406). In appendix 5, selected data from different types of studies have been compared.

Stroke mortality (43, 406) and incidence (43) have declined in most western countries during recent years. An increased survival in victims of stroke (43) might, however, lead to increasing rates of vascular dementia.

In our study, women had a higher proportion of MID/mixed dementia than men. This finding was unexpected as Alzheimer dementia of old age is thought to be more common in females, while MID/mixed dementia is more common in males (205, 390, 401). The Eurodem research programme also pointed to a male dominance in the prevalence of VaD (355), except for the age-group 80-89 years, where the Lundby study and the Mini-Finland study showed a female preponderance. The latter is in accordance with our finding. It may be that women develop vascular dementia later than men do, or that men with vascular dementia die earlier. Men had a higher proportion of secondary dementias, reflecting the fact that men generally have poorer physical health than women at these ages.

In younger age-groups subjects with dementia have been found to have lower survival rates than subjects without dementia, and subjects with VaD have poorer survival rates than subjects with AD (304, 442). It has, however, been hypothesised that the excess mortality from dementia diminishes in higher age-groups (297). The present study clearly shows that the increased mortality from dementia disorders also holds true in higher age-groups.
Comments on methods

The comparatively high rate of VaD in our study may be due to the following factors:

a) Diagnostic procedures

Previous epidemiological studies have used rather few laboratory investigations in the diagnosis of different causes of dementias (185), which makes it difficult to compare the proportions with those in this study. However, four recent studies by Rocca et al (354), Folstein et al (136), Livingston et al (263) and Evans et al (127) used detailed clinical diagnostic procedures, including CT-scanning in some cases, on subjects screened as demented in population surveys. The relative proportions of vascular dementia and Alzheimer's disease in two of these studies (136, 354) were similar to those found in our study.

With the criteria used in this study, the agreement between clinical and neuropathological diagnosis of AD has been reported to be 80-90% (35, 40, 87, 201, 219, 349, 411). The agreement between the clinical and pathological diagnosis of MID has generally been lower, between 50% and 61% (35, 201, 411). However, if MID and mixed dementias are grouped together, the agreement increases to 80-95% (35, 124, 201), and with the criteria used in this study, the diagnostic accuracy was 90% even for MID (124, 126). However, it has to be emphasised that clinico-pathological correlation studies have not been performed in samples from the general population. Furthermore, although the histopathological diagnosis is often stated to be the "golden standard" for a diagnosis of AD (227, 285) and VaD (278), it is unclear at present how the neuropathological manifestations of AD (227, 402, 403, 432) and VaD (97, 126, 151, 171, 210, 215, 266, 301, 355, 372, 395) are related to pathogenetic mechanisms and the development of dementia. Furthermore, extensive histopathological changes of AD (11, 87, 227, 307, 324, 399, 401, 402, 403, 432) and VaD (97, 307, 324, 372, 401) have been found in persons who show no clinical signs of dementia during life, and after the age of 80 the brain of a control without dementia may be difficult to distinguish from that of an age-matched patient with AD (227). SPs or NFTs have also been reported in a wide variety of conditions other than AD (159, 173, 402, 403), indicating that these changes may be unspecific markers of brain pathology. Finally, there are marked differences of opinion among neuropathologists regarding the histopathological diagnosis of AD (402, 433) and VaD (97, 278), tissue preparations used (433) and staining procedures (433), and according to the Khatchaturian criteria (227) an AD diagnosis is possible even in the absence of dementia.

In general, AD may be underdiagnosed clinically in cases with an atypical course, including focal symptoms (126), abrupt onset (134) and stepwise deterioration (134), suggesting MID, and in cases with coexisting medical illnesses, indicating secondary causes (159), and it may
be overdiagnosed due to the increased publicity and funding (40, 187) - in many scientific papers AD is used almost synonymously with the dementia syndrome - and as current clinical criteria may result in the inclusion of other dementias such as frontal lobe dementia, subcortical dementia and other primary degenerative dementias (298). Finally, in 4-12% of cases with a typical picture of AD, autopsy shows no or minimal pathology (182, 201, 227, 349, 402, 403).

VaD may be overdiagnosed (57, 167, 215, 216, 423), by both histological (56) and clinical (56, 216) criteria, as neither clinical nor pathological evidence of stroke or vascular disease necessarily means that they caused the dementia (57, 261, 266, 292, 401). With current criteria, patients with any form of dementia and a stroke will be given the clinical diagnosis of VaD (136, 263, 292). VaD may also be underdiagnosed (88, 187, 315). First, VaD may have an insidious onset and gradual course (88, 126, 134, 315, 412) and may be mistaken for AD. Second, many infarctions are clinically silent, without evidence of stroke or focal neurological symptoms and signs (97, 119, 151, 187, 250, 265, 315, 395), or may pass unnoticed for other reasons (292). Third, many infarcts are not detectable by CT (126, 139, 292, 294, 336, 407, 426). Fourth, cerebral areas can be damaged and non-functional although CT-scan imaging remains normal (177). Fifth, the symptoms used for the criteria of VaD in the present study were limited to definite focal neurological symptoms and signs. Sixth, 30% of the subjects with dementia did not have a CT-scan. Finally, we did not use as criteria other vascular factors that might cause dementia or contribute to it - such as white-matter lesions and severe cardiovascular diseases. It is, however, undoubtedly difficult to establish whether vascular disease caused, contributed to, or coincided with dementia (170, 171, 301), and we might have overestimated the diagnosis of VaD in cases of mixed VaD/AD. However, it is important to identify the vascular component as it might be amenable to treatment (170).

CT in the diagnosis of VaD has been questioned. CT may identify the presence of infarcts in patients with dementia (9) but this does not prove a causal relationship (215) and gives no information about the chronological sequence of the lesions (355). There is also the problem of determining which of the changes seen existed at the time of onset of dementia and which developed later (292), and which changes were merely co-incidental. It has been claimed that VaD may be overdiagnosed if infarcts on CT are used as a diagnostic marker (216), other have the opposite opinion (400). The finding in our study that infarcts on CT were significantly more common in subjects with dementia (28%) than in subjects without dementia (13%) supports the use of CT in the diagnostic procedure of VaD. In other studies, the prevalence of visible infarcts on CT in non-demented subjects has varied from 3% to 13% (193, 199, 268, 337), in unselected groups of demented subjects from 15% to 19% (193, 238), and in VaD from 14% to 96% (2, 59, 89, 126, 148, 199, 238, 268, 321, 336, 351, 384, 400, 412). Some studies have compared demented and non-demented subjects. Inzitari et al. (193) reported 15% in demented and 3% in non-demented subjects, London et al (268) reported 5% in AD,
14% in VaD and 6% in non-demented subjects, Jayakumar et al (199) reported 96% in MID and 13% in controls, Soininen et al (384) had 26% in MID, 2% in AD and 7% in controls. In clinically diagnosed Alzheimer's disease, the prevalence of infarcts on CT has varied from 0% to 30% (59, 89, 238, 268, 336, 384, 412), showing that the diagnosis of pure AD is often made even in the presence of infarcts on CT (251).

In the Framingham study, VaD was only diagnosed in subjects with both infarcts on CT and a history of focal neurological symptoms and signs, yielding a prevalence of 9% (216). If we had used the same criteria, our prevalence would have been 13%. However, their criteria are probably far too strict.

An international workshop organised by the National Institute of Neurological Disorders and Stroke (NINDS) and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN) recently proposed criteria for VaD (360). Our criteria are quite close to these criteria (359). However, the NINDS-AIREN criteria propose an arbitrary limit of 3 months for onset of dementia after stroke. This is difficult to apply in prevalence studies, in which dementia often has had its onset many years before examination. They also include senile leucoencephalopathy (=WMLs) among the vascular dementias. The inclusion of this criterion is important, as shown in this study (Paper IV), and should have given an even higher proportion of VaD if we had included it in our calculations (Paper I). Our criteria are also similar to those of Chui et al (74).

Other concomitant diseases are a quite common differential diagnostic problem in old age dementia (159, 219). The present study included detailed laboratory examinations. This report has taken the results from these into consideration for the aetiological diagnosis, but it was sometimes difficult to decide whether these disturbances had caused an irreversible neuronal loss or unmasked a pre-existing subclinical Alzheimer's disease or vascular dementia (366). However, the majority of "reversible" dementias develop a progressive course even after an initial period of improvement after treatment (243, 248, 340), and when abnormal findings occurred, for example hypothyroidism, depression or B\textsubscript{12}-avitaminosis, the course, the clinical picture and the outcome of treatment decided the diagnosis.

b) Sample

Factors related to the sample may be associated with the high age of the subjects and that institutionalised persons were included. Livingstone et al (263) and Evans et al (127) had a very low proportion of vascular dementia in their samples, but institutionalised people were not included. Livingstone et al (263) suggested that persons with vascular dementias might have more physical disabilities and thus might be more likely to be institutionalised, which is in agreement with our finding that those with VaD more often were institutionalised.
Furthermore, there was no difference in our sample between institutionalised and non-institutionalised persons regarding participation in the study, indicating that differences in participation with regard to this factor was not a major cause for the high prevalence of VaD.

c) Prevalence

The prevalence day was chosen as close as possible to the time when the subjects were 85.5 years old. Studies with the prevalence day set to a certain date include all people that are alive at that date. The examinations in question have, however, generally been performed during a period of 1-2 years after that date. During this time, losses due to death may be considerable in the oldest age-groups. If subjects with VaD have a higher mortality than those with AD, as suggested by the present study, it will lead to a comparatively higher loss due to death in subjects with VaD. This may be one explanation for the lower proportion of VaD in other population studies and the reported decrease in the proportion of VaD with age. The phenomenon of differential mortality may also affect the results in studies with two-phase designs. Evans' study had an extremely high prevalence of AD (127), but VaD may have been disproportionally common among those who died or were institutionalised during the 16-month interval between screening and examination (198).

IV. WHITE MATTER LESIONS

Comments on the results

The prevalence of WMLs

The prevalence of WMLs in non-demented subjects was 34%. This figure is compatible with that of Goto et al (152), who found 39% in the age-group 80-89 in a series of consecutive CT-examinations (including demented subjects), but higher than in normal controls (150, 193, 268, 347), which may be explained by the lower mean ages in the subjects and the exclusion criteria used in these studies.

The prevalence of WMLs in AD was 64%, which is higher than in studies of AD in younger age-groups (2, 33, 119, 150, 193, 268, 347) but similar to findings in AD of late onset (33). The clinical picture of dementia related to WMLs is similar to that of AD, which may result in the inclusion of subjects with dementia caused by WMLs in clinical studies of AD.
In younger age-groups, the rate of WMLs has generally been higher in vascular dementia than in AD (2, 119, 242). We found no such difference in 85-year-olds and it is possible that the difference diminishes with increasing age.

There was an association between the presence and severity of decreased attenuation and the occurrence of dementia, but not the severity of dementia. The latter is in line with Blennow et al. (33) and George et al. (150), but different from Erkinjuntti et al. (119), and indicates a complex relationship between dementia and WMLs. It may be that strategic lesions of subcortical pathways (170, 416) cause, or contribute to, dementia but that other factors determine the severity of dementia.

An overlap with normal ageing is also found in other conditions associated with dementia, e.g. senile plaques and neurofibrillary tangles in Alzheimer's encephalopathy (403) and cerebral infarcts in MID (97). Although the study showed an increased prevalence of WMLs in demented subjects, this does not establish a causative link. It still has to be determined whether the presence of WMLs contributes to the dementing process or if it is only an indirect sign of dementia or ageing processes. The cross-sectional design of the present study limits the possibilities of drawing conclusions about this.

WMLs have been proposed to represent a disease entity of their own, included among the vascular dementias (360). The finding that both infarcts on CT and WMLs independently contributed to dementia supports this opinion. If white matter dementia is included among the vascular dementias, these would cause or contribute to 85% of all dementias in the present study.

**WMLs and other mental disorders**

This study did not demonstrate an increased rate of WMLs in any other mental disorder than dementia. Most studies reporting an association between WMLs and late-onset psychosis or mood disorders were performed on MRI. WMLs on MRI may be both quantitatively and qualitatively different from those found on CT, and may reflect alterations in the distribution of intracerebral free water, which may occur in affective disorders (105, 331), rather than cell loss.

**WMLs and neuropsychological functioning**

The relevance of WMLs in normal elderly persons, as well as in demented subjects, has been disputed. Our results (Paper V), however, showed that both demented and non-demented subjects with WMLs, compared with demented and non-demented subjects without such lesions, showed impairments in neuropsychological functioning, predominantly visuospatial.
abilities. The results are comparable with those described in subcortical disorders (39, 52, 90, 144, 189), and in pure Binswanger's disease (142). Slowing of mental processes, here manifested as a reduction in perceptual speed in non-demented subjects with WMLs, is also a cardinal feature of subcortical disorders (90, 144). A common pathophysiological mechanism of subcortical disorders, including WMLs, may be a disruption of fronto-subcortical connections (3).

WMLs have been associated with hypertension (170, 416) and hypertension has been associated with impaired neuropsychological function (18, 38, 284, 430). Van Swieten et al. (409) found that cognitive decline in hypertensive individuals was associated with WMLs, while Schmidt et al. (373) did not corroborate this finding. A decline in neuropsychological performance in the elderly might be associated with hypertension, producing pathological changes in the white matter. The present study suggests that WMLs may be a cause of cognitive decline in non-demented elderly subjects, as hypothesised by Boone et al (44).

**Comments on the methods**

There were no differences between subjects who participated in the CT-examinations and those who refused with regard to a number of factors known to be related to the occurrence of WMLs, indicating that the participants were similar to the total group of 85-year-olds. However, the high refusal rate in the non-demented group makes it necessary to consider the question of representativity with caution.

Clinicopathological studies have constantly reported that WMLs on CT are related to the histopathological finding of marked demyelination and narrowing of the lumen of small penetrating arteries and arterioles in the white matter (14, 37, 149, 150, 152, 160, 211, 228, 242, 267, 271, 334, 347, 358, 364, 438). WMLs on MRI are often reported as being the same entity as WMLs on CT. However, WMLs on MRI correspond to several different histological findings, most often état crible (12, 13, 17, 22, 23, 42, 47, 48, 73, 113, 155, 204, 230, 293, 413), and often show no correlation with cognitive decline (160, 190, 226, 237, 256, 293).

MRI is thus more sensitive than CT but has a lower specificity (17, 73, 120, 126, 190, 204, 228, 256, 293, 301, 357) and WMLs on MRI may bear little relationship to the WM hypodensities seen on CT (169, 190, 256). The use of CT-scanning in this study probably resulted in more specific findings, but a lower prevalence of WMLs than if MRI had been performed.
CONCLUSIONS:

I. This study showed a high prevalence of dementia (30%) and other mental disorders (24%) in a representative sample of 85-year-olds. Those afflicted with dementia showed an increased risk of institutionalisation, and while only 1% of 85-year-olds without mental disorders were institutionalised 10% of those with mild dementia, 37% of those with moderate dementia and 88% of those with severe dementia were institutionalised. The findings have important implications for health planning.

A high rate of prescription of non-specific psychotropic drugs occurred in the population, yet only one-fifth of those depressed received antidepressants, and only one-tenth of those with psychotic disorders received neuroleptics.

II. Subjects with a clinical diagnosis of Alzheimer's disease more often had concomitant schizophrenic symptomatology, and subjects with mild dementia had an increased risk of depressive syndromes compared with non-demented subjects. Structural and/or neurochemical aberrations in these subjects may predispose to mental syndromes.

III. Among the subjects with dementia, a high proportion (47%) had vascular dementias. This might have important implications as these disorders might be amenable to treatment and prevention.

IV. Subjects with dementia in this study had a higher prevalence of white matter lesions (WMLs) than subjects without dementia, indicating the importance of these changes in the development of dementia. Both infarcts and WMLs on CT were independently associated with dementia. If dementias with white matter lesions are included among the vascular dementias, the proportion of subjects with vascular factors contributing to dementia will be over 80% in this age-group. WMLs were correlated to decrements of neuropsychological functioning in both demented and non-demented subjects.
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APPENDIX 1: PREVALENCE STUDIES ON DEMENTIA
APPENDIX 2: PREVALENCE STUDIES ON DEPRESSION
APPENDIX 3: PREVALENCE STUDIES ON PSYCHOSIS