

# Epidemiology of the dementias: recent developments and new approaches

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Dementia is an important cause of disability in elderly people. Given the increase in the proportion of elderly people in most countries, the number of patients with dementia will rise and the care of these patients will have a growing impact on the healthcare system and society. The past decade has seen many successes in epidemiological studies of the aetiology of chronic disorders including cardiovascular disease, cancer, and osteoporosis. In this review, new developments in the epidemiology of the dementias are discussed. Descriptive studies of the occurrence of dementia across different populations and time periods as well as studies of risk factors for dementia are reviewed. Dementia is a syndrome that can be caused by many conditions. As Alzheimer's disease is the predominant cause of dementia, accounting for at least half of the cases in most populations, epidemiological research has focused on this disorder.

## Geographical trends

Cross cultural comparison of the occurrence of disease has led to important clues to risk factors implicated in chronic disorders such as cardiovascular disease and cancer. The number of epidemiological studies on dementia is still small compared with these other chronic

disorders. However, several community based studies have considered the *prevalence* of dementia—that is, the number of patients with dementia alive in a defined population and time frame. These studies have been reviewed recently.<sup>1-3</sup> An important limitation of prevalence studies is that differences in occurrence and survival of disease in a population cannot be distinguished. They are of little value when comparing the risk of dementia across populations. Community based studies of the *incidence* of dementia—that is, the number of patients that are newly diagnosed in a defined population and time frame—are to be preferred.

At present, there are only a limited number of such studies available.<sup>4-17</sup> The table shows their general characteristics. In all studies, the diagnosis of dementia and Alzheimer's disease was in accordance with currently accepted criteria.<sup>18-19</sup> Figures 1 and 2 present age specific incidence rates of dementia and Alzheimer's disease. Up to the age of 75 years, there is little evidence for a large variation in dementia and Alzheimer's disease between studies. The incidence of Alzheimer's disease seems to be increased in the east Boston study<sup>16</sup>; however, this may be explained by the fact that the diagnosis of Alzheimer's disease was based primarily on psychometric testing.<sup>4</sup> There is considerable variation in the incidence of dementia and Alzheimer's disease between populations after the age of 75 years, which is not likely to be a result of differences in diagnostic criteria given the lack of variation up to the age of 75 years. However, the few subjects at risk in some studies, methodological problems related to non-response, competing mortality, and comorbidity complicating the diagnosis make it doubtful whether these variations truly reflect a difference in incidence of dementia between populations.

There is some evidence that the relative proportion attributed to the most common subtypes, Alzheimer's disease and vascular dementia, differ between populations.<sup>20</sup> In studies of Caucasian populations from Europe and North America, over 50% of all patients with dementia were attributed to Alzheimer's disease compared with only 12-30% to vascular causes.<sup>20</sup> In Asian populations, vascular dementia was found to be underlying the dementia in up to 60% of the patients.<sup>20</sup> In the

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General characteristics of community based studies on the age specific incidence of dementia and Alzheimer's disease

	No of subjects studied	Period of follow up (y)	Age range (y)
Europe:			
Lundby, Sweden <sup>5</sup>	3563	25	All
Gothenburg, Sweden <sup>4</sup>	385	4-5	70-79
Mannheim, Germany <sup>13</sup>	1912	7-8	65+
Bordeaux, France <sup>14</sup>	2792	3	65+
Liverpool, UK <sup>8</sup>	1070	3	65+
Nottingham, UK <sup>10</sup>	1042	4	65+
Cambridge, UK <sup>15</sup>	1195	2-4	75+
London, UK <sup>12</sup>	705	3	65+
North America:			
Rochester, USA <sup>11*</sup>	55000	25	All
New York, USA <sup>6</sup>	488	8	75+
Framingham, USA <sup>9</sup>	2117	10	65+
East Boston, USA <sup>16†</sup>	2312	4-3	65+
Asia:			
Hisayama, Japan <sup>17</sup>	828	7	65+
Beijing, China <sup>7</sup>	1090	3	60+

\*Although based on a medical register, the coverage of this register is such that it may be considered community based.

†Incidence is estimated based on a sample of 642 patients who received detailed clinical examination.

Figure 1 Comparison of age specific incidence of dementia in community based studies in Europe (A) and elsewhere (B).

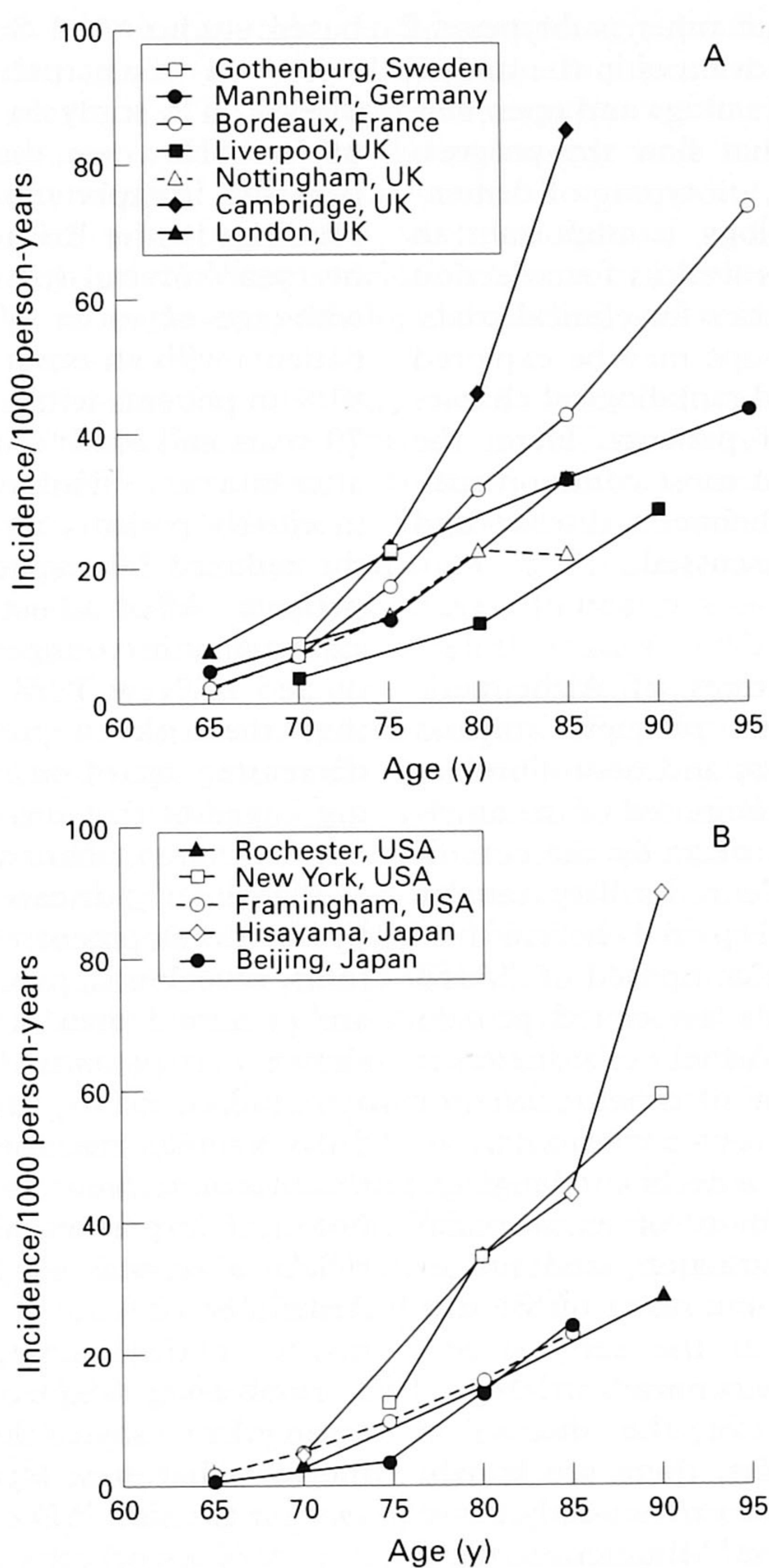
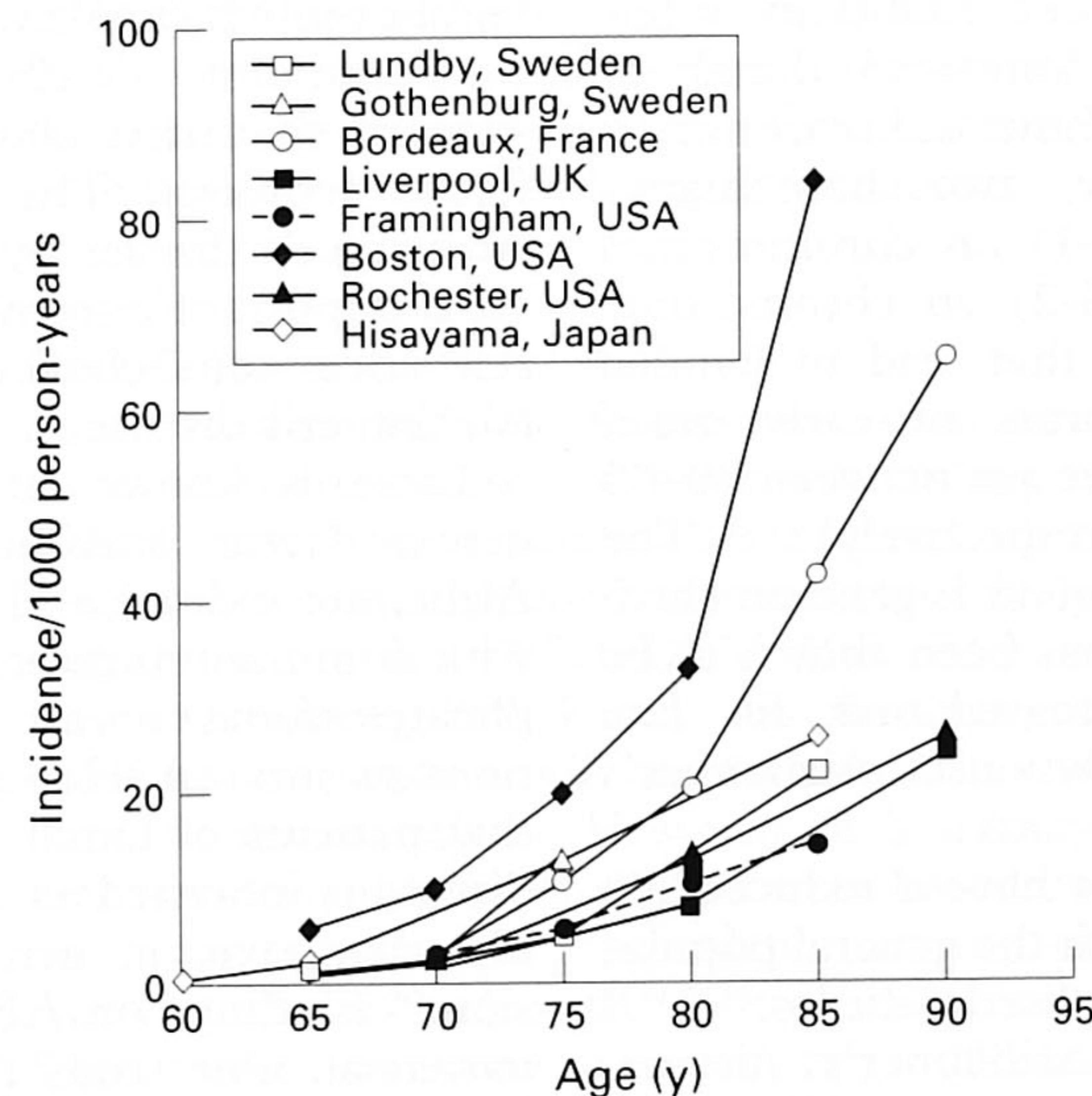


Figure 2 Comparison of age specific incidence of Alzheimer's disease in community based studies.



two Japanese studies of incident patients, vascular dementia constituted 40% and 60% of all dementia.<sup>7,17</sup> As the incidence of Alzheimer's disease was similar across populations, this suggests that the incidence of vascular dementia may be increased in Asian populations.<sup>7,17</sup> It may be speculated that genetic or environmental factors underlie the differences in incidence of vascular dementia across populations. However, there are two

important considerations. Firstly, vascular dementia may be underestimated in Caucasian populations as some prevalence studies in Caucasians have reported a proportion of vascular dementia up to 50%.<sup>4,21</sup> Secondly, an intrinsic problem when comparing different populations for the relative proportion of Alzheimer's disease and vascular dementia is the fact that the diagnosis of vascular dementia is based on the presence of dementia and cerebrovascular disease. The diseases may be related, but no causal relation between the vascular pathology and the dementia can be established in patients. This may bias the comparison of populations with different rates of vascular disease, as this would inevitably predict a higher proportion of vascular dementia in populations with a higher rate of vascular disease. As the clinical diagnosis of Alzheimer's disease is based on the exclusion of other causes of dementia, including vascular dementia, this may also affect the prevalence of Alzheimer's disease. Similar problems relate to the comparison of the frequency of subtypes of dementia between Caucasian and Afro-American populations. Because of the higher frequency of hypertension and stroke in Afro-Americans, an increased proportion of the vascular and the mixed Alzheimer and vascular type of dementia<sup>22</sup> would be expected. In the absence of biological markers and unequivocal clinical or morphological criteria, cross cultural comparisons of the risk of subtypes of dementia will be difficult to interpret.

### Time trends

Variation in incidence of dementia over time within a population may lead to hypotheses about environmental risk factors. Again, studies of the prevalence of dementia are less informative for this as they may be biased by differences in survival. Despite the lack of specific treatment, survival of patients may have improved.<sup>5,23,24</sup> There are only two long term follow up studies available which have monitored incidence of dementia over time. Data on the incidence of senile dementia over a 25 year period (1947–72) are available from a study conducted in Lundby, Sweden.<sup>5</sup> In this study, there was no evidence for a trend over time. Data on incidence collected in Rochester, Minnesota in the period 1960–84 suggested that changes in incidence of dementia may have occurred.<sup>11</sup> A higher incidence of dementia was found in the earliest (1960–4) as well as the latest (1980–4) period studied and was found to be limited to the very old. However, the increased awareness of dementing illness in the past decade may have influenced rates of diagnosis in the later period.<sup>11</sup> So far, studies of trends in the incidence of dementia over time have yielded few clues about the aetiology of the disease.

### Clinical characteristics

Clinical epidemiological studies in patients with heterogeneous disorders, such as

Alzheimer's disease and other subtypes of dementia, may lead to advances in the understanding of the pathophysiology and open new leads to interventions that slow the progression of disease. Further, subtyping of dementias according to aetiology is important in establishing prognosis as well as for selection of homogeneous case series for clinical trials. The existence of subgroups may be explored by studies on clinical and pathological characteristics and survival of patients. Here, the characteristics of the two most common subtypes of dementia, Alzheimer's disease and vascular dementia, are discussed.

#### ALZHEIMER'S DISEASE

Neuropathological features of Alzheimer's disease comprise neuritic plaques, amyloid angiopathy, neuronal loss, and neurofibrillary tangles. Amyloid fibrils composed of the amyloid protein (A4 protein) make up the core of the neuritic plaques. Neurofibrillary tangles consist of intraneuronal paired helical filaments, which are in part composed of altered forms of the microtubule associated protein tau. Although clinically Alzheimer's disease is a diagnosis by exclusion of other causes of dementia,<sup>18 19</sup> the disease is characterised by an impaired learning ability, a decline in language function, and deterioration of visuospatial skills.<sup>25</sup> Calculation, abstraction, and judgement are often affected, the onset of the disease is insidious, and in the early stages, changes in personality are common.<sup>18 19 25</sup>

Although the origin of the disease is unknown in most patients, there are known gene mutations that may cause an early onset form of Alzheimer's disease. Mutations in the  $\beta$  amyloid precursor protein (APP) gene on chromosome 21 have been found in a few families, which cause an autosomal dominant form of early onset Alzheimer's disease (onset < 55 years).<sup>26</sup> Recently, two homologous genes—presenilin 1 (PS-1) on chromosomes 14 and presenilin 2 (PS-2) on chromosome 1—have been identified that lead to familial autosomal dominant forms of early onset Alzheimer's disease (onset age between 30–55 years and 50–70 years respectively).<sup>27–29</sup> The  $\epsilon 4$  allele of the apolipoprotein E gene on chromosome 19 (APOE\*4) has been shown to be associated with an increased risk for late onset<sup>30 31</sup> as well as early onset Alzheimer's disease.<sup>32 33</sup>

Patients with dementia have a reduced life expectancy compared with the general population and other institutionalised patients.<sup>23 24 34 35</sup> Among patients with Alzheimer's disease, there are major differences in mortality.<sup>34</sup> The wide range in survival may in part be explained by differences in duration of disease at entry into the study. A meta-analysis of community, clinic, and nursing home based studies on survival showed mortality to be increased in men.<sup>34</sup> However, studies of prevalent cases may be biased as patients who die early in the course of disease are less likely to be included in the study, resulting in an overestimation of survival. Survival in incident cases has been considered in four community

based studies.<sup>4 6 8 24</sup> Survival was significantly worse in male patients with Alzheimer's disease in a study in Rochester,<sup>24</sup> but not in others.<sup>4 6</sup> However, the small sample size hampers the interpretation of the latter studies. Findings in the Rochester study suggest that five year survival (period 1975–84) decreases with age of onset of disease from 84% in patients with an onset at or before 69 years to 81% in patients with an onset between 70 and 79 years and to 40% in patients with an onset after 80 years.<sup>24</sup> However, the reduced survival in elderly patients may be a consequence of the reduced life expectancy in the late onset patients. After adjusting for the higher life expectancy in younger patients, a study conducted in New York (the Bronx), suggested that the risk of mortality increased with decreasing age of onset of disease.<sup>6</sup> This finding suggests that an earlier onset of disease may be more malignant.

Alzheimer's disease is often accompanied by the development of extrapyramidal symptoms, myoclonus, psychosis, seizures, aphasia, and primitive reflexes.<sup>36–39</sup> Several studies have shown that patients developing one of these symptoms tend to deteriorate to specific cognitive and functional end points more rapidly than those without these symptoms.<sup>36–40</sup> It is not clear at present whether these symptoms reflect a clinical subgroup of patients with Alzheimer's disease or whether they are merely markers of disease progression. The finding of an increasing frequency of these symptoms during the course of disease is compatible with the view that these factors are markers of disease progression.<sup>36</sup> On the other hand, the frequency of myoclonus and aphasia early in the course of disease is increased in patients of families in which Alzheimer's disease is linked to a mutation on chromosome 14.<sup>41–43</sup> This suggests that these clinical features reflect different aetiology. The ongoing dissection of Alzheimer's disease by its genetic causes may yield important information on the origin and relevance of concomitant pathology in Alzheimer's disease.

Little is known of the relation between genetic factors and mortality in patients with Alzheimer's disease. The number of patients with dominant mutations is small, which complicates studies on the relation of these mutations to survival. However, it has been shown that patients of families in which Alzheimer's disease is inherited as an autosomal dominant disorder have, in general, a worse progression.<sup>44</sup> Findings on APOE\*4 have been controversial. One study reported no association between survival and clinical characteristics,<sup>45</sup> whereas other studies suggest that APOE\*4 is associated with a slower progression and prolonged survival in patients with Alzheimer's disease.<sup>46–48</sup> The  $\epsilon 2$  allele of apolipoprotein E (APOE\*2) has been associated with an increased mortality in one study,<sup>48</sup> but this finding remains to be confirmed.

#### VASCULAR DEMENTIA

Vascular dementia is a syndrome that may be caused by several vascular lesions, including

ischaemic, hypoxic, and haemorrhagic brain damage.<sup>25</sup> The clinical diagnosis requires the presence of (a) dementia, (b) cerebrovascular disease evidenced by neuroimaging and by neurological symptoms, and (c) a temporal relation between the vascular disease and dementia.<sup>25</sup> Vessel occlusion seems to be the most common pathology underlying vascular dementia.<sup>25</sup>

Several clinical subtypes of vascular dementia have been recognised, including multi-infarct dementia, lacunar state, and Binswanger's disease.<sup>25</sup> Diagnosis of these subtypes of vascular dementia syndromes has been facilitated by the progress in neuroimaging.<sup>49</sup> Clinical-epidemiological studies with MRI are likely to play an important part in separating clinically and aetiologically relevant subgroups, especially in combination with genetic studies. Thus far, genetic and MRI studies have been successful in unravelling the aetiology of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).<sup>50 51</sup> This is an inherited disease associated with dementia, stroke and transient ischaemic attacks, migraine with aura, and mood disorders.<sup>50 51</sup> Abnormalities on MRI are found in the subcortical white matter and basal ganglia and can be detected before the clinical expression of the disease.<sup>50 51</sup> Molecular research suggests that CADASIL is linked to a gene on chromosome 19.<sup>50</sup>

Studies on the survival of patients have consistently shown a reduced life expectancy for patients with vascular dementia compared with the general population. Survival is worse than in patients with Alzheimer's disease.<sup>21 23 34 35 39</sup> The number of studies on predictors of survival for vascular dementia is still small, but male sex,<sup>39 52</sup> low education,<sup>52</sup> advanced disability,<sup>39</sup> and primitive reflexes<sup>39</sup> have been associated with poorer prognosis.

### Risk factors

Most studies of risk factors for dementia have focused on the commonest subtype, Alzheimer's disease. Studies conducted before 1991 have been reviewed and collaboratively reanalysed by the EURODEM Risk Factors Research Group.<sup>53-60</sup> Here, the findings of more recent studies will be evaluated in the light of this reanalysis. However, it is important to realise that most studies were based on the comparison of prevalent cases of Alzheimer's disease with control subjects.<sup>53</sup> Such studies are prone to various types of bias. Selection bias may have occurred due to mortality in patients related to the risk factor studied. Assessment of exposure to the risk factor has often been based on information from surrogates, which may introduce error. Further, differential misclassification in exposure to risk factors between cases and controls may have occurred, as informants of patients may have been better at recalling exposures than controls. The relation of most risk factors for Alzheimer's disease remains to be confirmed in follow up studies of incident patients, in

which the exposure state is measured before the onset of disease.

### AGE AND SEX

The risk of dementia and Alzheimer's disease increases strongly with age (see figs 1 and 2),<sup>1-3</sup> suggesting that genetic and environmental factors which influence aging of the brain may play an important part. Two studies of the incidence of Alzheimer's disease found that the disease occurred more often in women than men,<sup>5 17</sup> but most studies show a similar incidence in men and women.<sup>4 8 9 11 14</sup> Vascular dementia has been found to be more frequent in men than women,<sup>4 14 17</sup> which probably reflects the higher frequency of vascular disease in men. The incidence of vascular dementia in men and women increased with age in the long term follow up study conducted in Lundby.<sup>5</sup> By contrast, an increase in incidence of vascular dementia with age was found only in women in the study conducted in the Bordeaux area in France.<sup>14</sup> However, the number of patients studied was small.

### GENETIC RISK FACTORS

Alzheimer's disease aggregates within families of patients with early and late onset of disease.<sup>54</sup> Several genes (APP, PS-1, PS-2) have been identified that are involved in the autosomal dominant forms of early onset Alzheimer's disease.<sup>26-29</sup> However, the role of these genes in late onset Alzheimer's disease, which concerns the vast majority of patients in the population, is limited. In the patients with late onset disease, the APOE gene on chromosome 19 seems to play a part.<sup>30-32</sup> Other forms of dementia including vascular dementia,<sup>61 62</sup> Lewy body disease,<sup>63</sup> and Creutzfeldt-Jakob disease<sup>64</sup> have also been associated with APOE\*4. Further, APOE\*4 has been associated with decreased cognitive function and increased rates of cognitive decline in the general population.<sup>65-68</sup>

Despite the fact that many studies have consistently shown an increased risk of Alzheimer's disease for APOE\*4 carriers,<sup>69</sup> some questions remain to be clarified to identify clinically relevant risk groups. There is still controversy about whether the risk associated with the APOE\*4 allele may be modified by sex,<sup>70-72</sup> ethnicity,<sup>73-75</sup> age,<sup>72 76</sup> or family history of dementia.<sup>33 72 77</sup> Although findings of two studies are compatible with modification of the risk of Alzheimer's disease for APOE\*4 carriers by sex,<sup>70 72</sup> one study failed to show evidence for interaction.<sup>71</sup> Among African and Afro-American populations, the risk associated with APOE\*4 is unclear as a lack of association between APOE\*4 and the risk of Alzheimer's disease has been found in some studies<sup>73 75</sup> but not in others.<sup>74</sup> Several studies found the relation between APOE\*4 and Alzheimer's disease to be absent in the very elderly patients.<sup>76 78</sup> Some studies have suggested that the strongest effect of APOE\*4 occurs in those with a positive family history.<sup>33 77</sup> A meta-analysis on the modification of the strength of association between APOE\*4 and the risk of Alzheimer's disease

by age and family history of dementia showed that the APOE\*4 allele frequency was highest among patients with familial Alzheimer's disease, the APOE\*4 frequency being 0.48 (95% confidence interval (95% CI): 0.45–0.51) in those with late onset and 0.42 (95% CI: 0.36–0.48) in those with early onset of disease.<sup>69</sup> The APOE\*4 allele frequency was significantly higher in patients with late onset sporadic Alzheimer's disease (APOE\*4 frequency: 0.37; 95% CI: 0.35–0.39) than in patients with early onset sporadic disease (APOE\*4 frequency: 0.28; 95% CI: 0.23–0.33).<sup>69</sup> This finding suggests that the risk of disease may be modified by age in patients with sporadic Alzheimer's disease.

Another issue that remains to be resolved is the association of Alzheimer's disease with the APOE\*2 allele. Several studies noted a lower frequency of the APOE\*2 allele in patients with Alzheimer's disease, suggesting that there may be a protective effect of APOE\*2.<sup>32 79</sup> However, an increased risk for carriers of APOE\*2 was found in an Italian,<sup>80</sup> a Dutch,<sup>48</sup> and an Afro-American population.<sup>74</sup> There are several possible explanations for the differences in association between Alzheimer's disease and APOE\*2 across populations, including linkage disequilibrium with another gene and modification by other genetic and environmental factors.<sup>48</sup> The discrepancies may also be a result of the reduced survival of patients with APOE\*2.<sup>48</sup> As most studies were based on prevalent cases, APOE\*2 carriers may have been selectively removed from the patient series over time. This may have resulted in an apparent decrease of the APOE\*2 allele frequency. In a similar way, the increased survival for patients with Alzheimer's disease with APOE\*4 that has been found in some studies may have led to an overrepresentation of APOE\*4 carriers in patients with Alzheimer's disease.<sup>46–48</sup> Although it is unlikely that the relation between APOE\*4 and Alzheimer's disease can be explained fully by survival effects, reduced mortality in APOE\*4 carriers may have led to an overestimation of the risk of Alzheimer's disease associated with the APOE\*4 allele.<sup>48</sup>

The mechanism through which APOE affects the risk of Alzheimer's disease and other types of dementia remains to be elucidated. The APOE\*4 allele has been implicated in various aspects of Alzheimer's disease pathology including  $\beta$  A4 amyloid deposition in senile plaques as well as in microtubule instability and paired helical filament formation.<sup>30 81</sup> APOE\*4 has also been shown to increase the risk of atherosclerosis, which may explain its association with vascular dementia.

#### DOWN'S SYNDROME

The increased risk of Alzheimer's disease in people with Down's syndrome has long been recognised. Alzheimer pathology has been found in most elderly patients with Down's syndrome.<sup>82</sup> When pooling and reanalysing the early case-control studies, there was considerable evidence for familial aggregation of

Down's syndrome and both early and late onset Alzheimer's disease,<sup>54</sup> but recent studies of patients with Alzheimer's disease have failed to show a significant association.<sup>83–89</sup> However, the negative findings may be a result of the low statistical power of individual studies.

As the frequency of Alzheimer's disease in the population is considerably higher than the frequency of Down's syndrome, studies of family history of dementia in patients with Down's syndrome have a higher statistical power. Although the early studies on family history did not yield consistent results,<sup>90 91</sup> a recent study has shed new light on this issue.<sup>92</sup> The study showed an increased risk of dementia in mothers of patients with Down's syndrome, but not in fathers, suggesting that non-dysjunction of chromosomes in the mother may play a part in familial aggregation of Down's syndrome and Alzheimer's disease.<sup>92</sup> The risk of dementia in mothers was increased only when the mother was younger than 35 years old at the birth of the child with Down's syndrome.<sup>92</sup> This finding suggests that the association is not explained by an increased risk of non-dysjunction with advanced maternal age but that other factors are involved. Because familial aggregation of Down's syndrome and Alzheimer's disease has been found to be strongest in those with a positive family history, it is possible that genetic factors may be implicated.<sup>93</sup>

#### PARKINSON'S DISEASE AND LEWY BODY DISEASE

Alzheimer's disease, Parkinson's disease, and Lewy body disease share several pathological features. The Lewy body and Alzheimer pathology can be found in each of these disorders. Dementia, a cardinal feature of Alzheimer's disease and Lewy body dementia, is often found in patients with Parkinson's disease.<sup>25 94</sup> There is some evidence for a common genetic origin of these disorders. Early studies were compatible with familial aggregation of Alzheimer's disease and Parkinson's disease,<sup>54</sup> being strongest in the families of patients with a positive family history of dementia.<sup>93</sup> Although more recent studies failed to confirm familial aggregation of these disorders,<sup>83–85 88 89</sup> the results of molecular genetic research suggest that they may have a common genetic origin. An increased risk of both Alzheimer's disease and Lewy body dementia has been associated with the APOE gene.<sup>30–33 63</sup> In recent studies, CYP2D6B, a gene that has been associated with Parkinson's disease and Lewy body disease, has also been associated with the Lewy variant of Alzheimer's disease and with synaptic pathology in Alzheimer's disease.<sup>95 96</sup> It is not yet clear whether any of these findings may explain familial aggregation of these disorders.

#### MATERNAL AGE AT BIRTH

As a corollary of the findings on Down's syndrome and family history of Down's syndrome, parental age has been studied as a potential risk factor for Alzheimer's disease. The findings are inconsistent. Some studies have suggested an association with late maternal age,<sup>55 85 88</sup> some found a significant increase

in risk for young maternal<sup>55-57</sup> and young paternal age,<sup>86-87</sup> and some found no evidence for an association at all.<sup>55-59</sup> Although young parental age has been associated with a moderate increase in risk of Down's syndrome, it seems unlikely that the strong association of Alzheimer's disease with young maternal and paternal age can be explained by an increase in risk of chromosome 21 non-dysjunction in meiosis at an early age.<sup>55</sup>

#### HEAD TRAUMA

Repeated head trauma in boxers has been associated with dementia pugilistica. The similarity in pathology of dementia pugilistica to the Alzheimer pathology has led to the hypothesis of a common pathogenesis of Alzheimer's disease and dementia. Early epidemiological studies were remarkably consistent in showing that patients were more often exposed to head trauma in the past than were controls, although the differences were not always significant.<sup>56</sup> Of the recent studies, three reported a significant increased risk of Alzheimer's disease after head trauma,<sup>89-98</sup> and four did not.<sup>83-85,88</sup> Studies of the history of head trauma have all been hampered by recall bias. Relatives of patients may have been more likely to remember head injuries that occurred in the past than relatives of controls. One prospective follow up study based on data obtained from the Rochester medical records showed only a slight and non-significant increase in risk.<sup>56</sup> However, a recent study suggests that the association may be modified by the presence of the APOE\*4 allele.<sup>100</sup> An increased risk of Alzheimer's disease after head trauma was only found in carriers of the APOE\*4 allele.<sup>100</sup> Any bias in recalling head trauma would be expected to be independent of APOE genotype and this finding, if confirmed, lends strong support to a relation between head trauma and Alzheimer's disease in the subgroup of cases who are APOE\*4 carriers. Regarding the biological mechanism, recent experimental studies suggested that the expression of  $\beta$  amyloid and interleukin 1 are increased after head trauma and that head trauma may be related to Alzheimer's disease through the induction of an acute phase response.<sup>101</sup>

#### DEPRESSION

Early studies suggested that a history of depression may be a risk factor for Alzheimer's disease.<sup>58</sup> The risk of Alzheimer's disease increased for those treated for depression 10 years or more before the first symptoms of dementia, suggesting that the depression was not simply a consequence of the dementia.<sup>58</sup> A similar association was present in a follow up study, in which the history of depression before the onset of disease was assessed from medical records.<sup>58</sup> Two recent studies showed no relation between depression and Alzheimer's disease,<sup>83-89</sup> but another reported a non-significant increase in risk of Alzheimer's disease in subjects with a history of depression in the previous three years.<sup>86</sup> Familial aggregation of depression has been reported in

patients with Alzheimer's disease and a positive family history of dementia.<sup>102</sup> This suggests that genetic factors may underlie the relation.<sup>102</sup> However, it remains to be excluded that depression is merely an early sign of Alzheimer pathology.

#### THYROID DISEASE

There is some evidence from the early studies of risk factors for Alzheimer's disease for an increased risk of disease in patients with hypothyroidism.<sup>57</sup> Further, an association between Alzheimer's disease and autoimmune thyroid disease has been reported in Down's syndrome and familial Alzheimer's disease.<sup>103,104</sup> None of the recent studies has confirmed the association with thyroid disease.<sup>83-88,89</sup> However, these studies were based on data from informants. One study on the history of thyroid disease based on medical records suggested that the risk of Alzheimer's disease was decreased for patients with Graves' disease, whereas there was a non-significant increase in risk for patients with myxoedema.<sup>105</sup> These findings and their pathophysiological importance remain to be clarified.

#### VASCULAR FACTORS

In recent years, the interest in vascular causes of dementia has increased, partly because there may be opportunities for prevention and treatment for this type of dementia. By definition, vascular disease and its risk factors must be present in patients with vascular dementia.<sup>25</sup> Factors that have been implicated in the risk of vascular dementia include hypertension, diabetes mellitus, and cardiovascular disease.<sup>106</sup> The mechanism through which these factors lead to dementia is unclear. Vascular factors may also be involved in Alzheimer's disease.<sup>106</sup> However, their role is difficult to quantify as patients with vascular disease are less likely to be diagnosed as cases of Alzheimer's disease.<sup>18,19</sup> White matter lesions have been found in increased frequency in patients with Alzheimer's disease in some studies but not in others.<sup>107,108</sup> Although these lesions have been associated with atherosclerosis,<sup>109</sup> they are not specific and may reflect cerebral atrophy and amyloid angiopathy in patients with Alzheimer's disease.<sup>107,108</sup> There is evidence from one MRI study that suggests that arteriolosclerosis may be specific for patients with late onset Alzheimer's disease.<sup>108</sup>

#### ANTI-INFLAMMATORY DRUGS

From experimental studies, there is increasing evidence that acute and chronic inflammatory processes play an important part in the pathophysiology of Alzheimer's disease.<sup>110,111</sup> Novel findings that may have clinical relevance are the inverse relations between Alzheimer's disease and past use of anti-inflammatory drugs and with rheumatoid arthritis, a disorder for which these drugs are often prescribed.<sup>84,89,112-114</sup> As the only follow up study failed to show a relation between rheumatoid arthritis and Alzheimer's disease,<sup>115</sup> a possible protective effect of anti-inflammatory drugs remains to

be clarified. Preliminary evidence showing that cognitive decline may be less in subjects taking indomethacin than in control subjects, indicates that further studies may be of interest.<sup>116</sup>

#### OESTROGEN REPLACEMENT THERAPY

Oestrogen may be implicated in Alzheimer's disease in several ways. Improvement of cerebral blood flow, direct stimulation of neurons, development of gliocytes, and suppression of apolipoprotein E have been suggested.<sup>117</sup> However, findings of epidemiological studies have been controversial. One study, based on computerised pharmaceutical records, did not show evidence for a relation,<sup>118</sup> whereas two studies based on anamnestic data suggested a protective effect of oestrogen replacement therapy.<sup>119 120</sup> There are important methodological problems which make the interpretation of the latter studies difficult. In one, a follow up study, based on direct interviews before onset of disease, the diagnosis of Alzheimer's disease at follow up depended on mortality records.<sup>119</sup> Mortality records have been shown to be unreliable for the ascertainment of patients with Alzheimer's disease. In the other study, the history of oestrogen use was obtained from informants for cases of Alzheimer's disease but from the control women directly.<sup>120</sup> Lack of knowledge of the use of oestrogens by the informant may explain part of the inverse relation found. Although some experimental studies on oestrogen suggest a beneficial effect,<sup>117</sup> there is no convincing evidence from epidemiological studies confirming such a role of oestrogen in Alzheimer's disease.

#### SMOKING HISTORY

Early epidemiological studies suggested an inverse association between Alzheimer's disease and history of smoking,<sup>59</sup> but recent studies have yielded equivocal results. The association between smoking and Alzheimer's disease was found to be absent in three studies,<sup>88 89 121</sup> inverse in two,<sup>122 123</sup> and positive in one.<sup>86</sup> The inverse association seemed to be related to social class in one study.<sup>123</sup> The results of a recent meta-analysis were compatible with a decreased risk of Alzheimer's disease in smokers.<sup>124</sup> There is some evidence that genetic factors, including the APOE gene, may alter the association between smoking and Alzheimer's disease.<sup>93 125</sup> The inverse relation between smoking and Alzheimer's disease was found to be limited to those with the APOE\*4 allele that had a positive family history.<sup>93 125</sup> However, modification of the relation between smoking and Alzheimer's disease by APOE has not been confirmed in other studies.<sup>126</sup>

Experimental studies of rats and rabbits have suggested that nicotine may improve memory and cognition.<sup>127</sup> Moreover, blockade of nicotinic receptor function may produce a significant cognitive impairment in humans<sup>128</sup> and clinical trials have suggested that nicotine and nicotine derivatives may improve information processing and attention in patients with Alzheimer's disease.<sup>129 130</sup> However, there was

no evidence for improvements in memory or cognition.<sup>129 130</sup> This suggests that nicotine or its derivatives modifies a rather limited spectrum of the clinical course of the disease.

Most studies of Parkinson's disease have also reported an inverse association with smoking.<sup>131</sup> By contrast with the findings on Alzheimer's disease and Parkinson's disease, the risk of vascular dementia was found to be increased for subjects that smoked,<sup>106</sup> suggesting a different effect of smoking in these disorders, rather than a general mechanism between smoking and dementia.

#### ALCOHOL

There was no evidence for an increase in risk of Alzheimer's disease in people with a moderate alcohol intake in a reanalysis of early case-control studies of Alzheimer's disease.<sup>59</sup> Also, no relation was found between alcohol consumption and Alzheimer's disease in two recent studies including one follow up study.<sup>89 122</sup> These findings should be treated with caution. Cases with higher alcohol intake may have been excluded when applying the criteria for probable or possible Alzheimer's disease,<sup>18 19</sup> leading to an underestimation in risk. Indeed, alcohol misuse has been associated with a significant increased risk of dementia<sup>132</sup> and Alzheimer's disease<sup>85</sup> in two population based studies.

#### OCCUPATIONAL EXPOSURE

Findings on occupational exposure to solvents have been controversial. No significant increased risk for occupational exposure to solvents and lead was found when pooling the early studies.<sup>60</sup> However, in the pooled analysis frequency of exposure was low and exposure definition was imprecise.<sup>60</sup> Two recent case-control studies have reported an association with occupational exposures.<sup>89 133</sup> In one study, an increased risk of Alzheimer's disease was found for subjects exposed to glues and pesticides.<sup>89</sup> Another study suggested a statistically significant increase in risk of Alzheimer's disease for men exposed to solvents such as benzene, toluene, phenols, alcohols, and ketones.<sup>133</sup> Studies on subjects exposed occupationally to solvents have suggested that risk of neurological symptoms may be modified by heavy alcohol consumption.<sup>134</sup> Whether the increased risk for Alzheimer's disease depends on the alcohol consumption or some other occupational exposure is not known at present.

#### ALUMINUM

There has been extensive debate on the question whether aluminum is implicated in the aetiology of Alzheimer's disease. The initial epidemiological studies were instigated in response to the finding of aluminum in neuritic plaques and tangle-bearing neurons. However, more recent studies of the association between aluminum and the Alzheimer pathology have yielded contradicting results.<sup>135</sup> On the other hand, there is growing evidence from experimental studies that aluminum may influence the conformation of both amyloid and neurofibrillary tangles.<sup>136-138</sup>

Follow up studies of the presence of Alzheimer pathology in the brains of patients who were on dialysis and exposed to high doses of aluminum have not been conclusive.<sup>139 140</sup> Epidemiological studies on the association between aluminum in drinking water and the risk of Alzheimer's disease have been reviewed recently.<sup>141</sup> With the exception of one study,<sup>88</sup> findings have been consistent in suggesting an increased risk of Alzheimer's disease with increasing aluminum concentration in drinking water.<sup>141 142</sup> However, the possibility of bias in present studies still outweighs the evidence for causal inference.<sup>141</sup> Studies that have considered the role of aluminum products such as antacids and antiperspirants have yielded equivocal results.<sup>84 89</sup> Supporting a role of aluminum in Alzheimer's disease was the finding of a lower level of cognitive functioning among miners treated with aluminum powder<sup>143</sup> and the finding of a slower progression of the disease in patients with Alzheimer's disease treated with aluminum chelating drugs.<sup>144</sup>

Despite the strong evidence from experimental studies that aluminum may be implicated in the Alzheimer pathology and progression of the disease, there are many questions to be answered from an epidemiological point of view. An issue that complicates the interpretation of the negative studies is the possibility that the effect of aluminum may depend on an interaction with other environmental factors. For instance, the risk of Alzheimer's disease associated with aluminum in drinking water may be influenced by the pH<sup>142</sup> or the presence of silicon.<sup>145</sup> Aluminum concentrations in serum and bone from cases of Alzheimer's disease are not raised suggesting that aluminum exposure and absorption is similar in patients with Alzheimer's disease and controls.<sup>146 147</sup> However, it is conceivable that genetic factors<sup>148</sup> or other (patho)physiological factors (for example, head trauma) may enable aluminum to enter the brain. Thus the increase in risk of Alzheimer's disease associated with aluminum may be present only in a subgroup of patients. These are issues that can only be considered in large scale epidemiological studies.

#### EDUCATION

It has been suggested that highly educated subjects have a lower risk of Alzheimer's disease and other types of dementia.<sup>149</sup> However, this finding was based on prevalent cases.<sup>149</sup> Two community based studies of incident cases failed to show an association of education with risk of Alzheimer's disease, suggesting that survival and selection bias may explain the earlier results.<sup>150 151</sup> Recent studies have produced conflicting results. Higher educational attainment was associated with an increased mortality<sup>152</sup> but a less severe stage of disease at the time of presentation in patients with Alzheimer's disease.<sup>153</sup> A relation between risk of vascular dementia and lower education levels was also found in a study of incident cases.<sup>151</sup> This finding may be

explained by the relation between low socio-economic class and vascular disease.

#### Discussion

By contrast with epidemiological studies of other chronic disorders, cross cultural studies have not led to important clues to the aetiology of dementia or any of its subtypes. There may be differences in the risk of vascular dementia between populations, but comparative studies of geographical and time trends are difficult to interpret because of the lack of biological markers and unique clinical features for the subtypes of dementia. Cross cultural comparison of studies of Alzheimer's disease showed no evidence for the existence of risk factors that are to be found predominantly in some populations but not in others. The risk factors for Alzheimer's disease seem to be ubiquitous.

Aetiological studies have uncovered some putative risk factors for Alzheimer's disease. There is growing evidence that several disorders including Down's syndrome, Parkinson's disease, depression, head injury, and perhaps thyroid disease may be associated with an increase in the risk of Alzheimer's disease. Familial aggregation of Alzheimer's disease with Down's syndrome, depression, and perhaps Parkinson's disease suggests that there may be a common genetic factor underlying these disorders in at least a subgroup of patients. As to environmental factors, the influence of alcohol and smoking is still controversial. Given the widespread exposure to aluminum through food products and drinking water, the relation between aluminum and Alzheimer's disease deserves further attention.

Epidemiological research on Alzheimer's disease is far from its limits. Most studies of risk factors for this disease have been small, whereas risk factors were rare.<sup>53</sup> The validity of studies has been compromised by anamnestic data collected through surrogate informants. Long term follow up studies, that are currently ongoing, will overcome these problems. Non-response, competing mortality, and comorbidity complicating the diagnosis, in particular in elderly people, will be challenges to overcome in these studies. However, advances in epidemiological research will not depend only on improved methodology. Recent epidemiological studies have led to preliminary findings of a protective effect of anti-inflammatory drugs and perhaps oestrogen replacement therapy that may prove to be of clinical relevance. Progress in the understanding of the genetics of Alzheimer's disease and other types of dementia has opened new possibilities for epidemiological studies on the risk associated with these genetic factors. Firstly, the risk of Alzheimer's disease associated with the various genetic factors identified including APOE remains to be quantified in follow up studies of incident cases. Secondly, the possibility of interaction between genetic and environmental risk factors needs to be studied, as the strength of association between an environmental factor and the risk of disease may

depend on the presence of a genetic factor.<sup>93</sup> Conversely, the effect of the genetic factor on the risk of Alzheimer's disease may be conditional on the presence of other genetic and environmental risk factors.<sup>93</sup> For APOE, there is some evidence for synergistic effects of APOE\*4, head trauma, and cholesterol and antagonistic effects of APOE\*4 and smoking with regard to the risk of Alzheimer's disease.<sup>72 100 125</sup> Interaction of APOE with other possible risk factors including vascular factors needs to be studied further. As pathological and molecular biological research proceeds, Alzheimer's disease and other types of dementia are likely to be dissected further into aetiological relevant subgroups.

CMvD is supported by grants of the Netherlands Organization for Scientific Research (NWO) and the Netherlands Institute for Health Sciences (NIHES). ACJW Janssens and AJC Slooter are acknowledged for helpful discussions of the manuscript.

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