Stability of the preclinical episodic memory deficit in Alzheimer’s disease

Lars Bäckman,1,2,3 Brent J. Small2,4 and Laura Fratiglioni2,3

1Department of Psychology, Uppsala University, Uppsala, 2Stockholm Gerontology Research Center and 3Division of Geriatrics, NEUROTEC, Karolinska Institute, Stockholm, Sweden and 4Department of Gerontology, University of South Florida, Tampa, Florida, USA

Correspondence to: Lars Bäckman, Stockholm Gerontology Research Center, Box 6401 S-113 82 Stockholm, Sweden
E-mail: lars.backman@neurotec.ki.se

Summary

We sought to determine the course of the preclinical episodic memory deficit in Alzheimer’s disease. Using data from a population-based study, we compared persons who developed Alzheimer’s disease (n = 15) with persons who were non-demented (n = 105) 6 and 3 years prior to the diagnosis of dementia. Participants were tested on tasks assessing episodic memory (free recall and recognition of words) and short-term memory (digit span). The incident Alzheimer’s disease cases performed more poorly than their non-demented counterparts both 3 and 6 years before diagnosis on recall and recognition. There were no group differences in either forward or backward digit span. The selective impairment of episodic memory before the diagnosis of Alzheimer’s disease is consistent with the view that early changes in the hippocampal complex play an important role in the memory deficit.

The magnitude of these deficits appears to be quite stable, at least up to 3 years before diagnosis. This may reflect the fact that those biological events that eventually result in the appearance of amyloid plaques and neurofibrillary tangles accumulate at a relatively slow rate.

Keywords: preclinical Alzheimer’s disease; episodic memory; recall; recognition

Abbreviations: MANOVA = multivariate analysis of variance; MMSE = Mini-Mental State Examination

Introduction

Several reports have documented cognitive deficits in persons who will develop Alzheimer’s disease prior to diagnostically significant cognitive, behavioural and social changes (Masur et al., 1994; Jacobs et al., 1995; Small et al., 1997). Such findings are vital in characterizing the insidious transition from normal ageing to dementia. Preclinical deficits in Alzheimer’s disease have been demonstrated in multiple cognitive domains, including psychomotor speed (Masur et al., 1994), verbal ability and reasoning (Jacobs et al., 1995) and visuospatial skill (Small et al., 1997). However, the most pronounced and consistent cognitive deficits in preclinical Alzheimer’s disease are seen for tasks assessing episodic memory (Hodges, 1998; Grober et al., 2000). This form of memory involves conscious retrieval of information acquired in a particular place at a particular time (Tulving, 1983). In the laboratory, episodic memory is typically assessed by having subjects recall or recognize some information encountered in the experimental setting (e.g. lists of words).

Episodic memory deficits in persons who will develop Alzheimer’s disease have been observed for both verbal (Linn et al., 1995; Tierney et al., 1996) and non-verbal (Fuld et al., 1990; Small et al., 1997) materials, as well as in different retrieval conditions, including free recall (Howieson et al., 1997; Grober et al., 2000), cued recall (Linn et al., 1995; Bäckman and Small, 1998) and recognition (Fuld et al., 1990; Small et al., 1997). The finding that episodic memory deficits in preclinical Alzheimer’s disease are marked and widespread is consistent with both histopathological (Braak and Braak, 1995; Van Hoesen et al., 1999) and morphological (Fox et al., 1996; Laakso et al., 1998) evidence that some of the earliest brain changes in this disease occur in the hippocampus and related structures. These regions have been
strongly implicated in episodic memory in both lesion (Squire, 1987; Vargha-Khadem et al., 1997) and brain imaging (Nyberg et al., 1996; Schacter et al., 1996) studies.

The time between initial assessment and diagnosis in studies demonstrating preclinical memory deficits in Alzheimer’s disease typically ranges between 2 and 3 years, although such deficits have been documented for longer periods (Fuld et al., 1990; Yoshitake et al., 1995). However, considerably less is known about the progression of memory deficits before the diagnosis of Alzheimer’s disease, as most of the relevant studies have included only one preclinical measurement point. There is evidence from both family-based (Fox et al., 1998) and clinical (Rubin et al., 1998) studies that patients in a preclinical phase of Alzheimer’s disease exhibit a precipitous cognitive decline during the period just preceding diagnosis. Whether those who will develop Alzheimer’s disease show disproportionate cognitive decline for a longer period before diagnosis remains unknown. Such knowledge is important to further our understanding of the course of the early development of Alzheimer’s disease.

The purpose of this research was to extend our knowledge concerning the course of the preclinical phase of Alzheimer’s disease, with particular focus on memory functioning. Persons from a population-based study were examined on three occasions over 6 years. On the last occasion, 15 individuals were diagnosed with Alzheimer’s disease, although the entire study sample (n = 120) was non-demented on the first two occasions of measurement. This design enables comparison of the accuracy of memory tests in predicting the development of Alzheimer’s disease 3 and 6 years prior to diagnosis, and the results provide novel information about whether preclinical Alzheimer’s disease is characterized by accelerated memory decline for a relatively long time before diagnosis. A related issue of interest is whether difference scores for memory performance (i.e. score 6 years before diagnosis minus score 3 years before diagnosis) are as effective as static performance scores in signalling an impending dementia disease. Unfortunately, missing data at the time of diagnosis precluded group comparisons of memory scores at that time point.

A final objective concerned the predictive accuracy of different types of episodic memory tests. Evidence is mixed with regard to which specific memory tests are most effective in identifying those who will develop Alzheimer’s disease. Some research suggests that tests that involve little support at retrieval (e.g. free recall) are most predictive of incident Alzheimer’s disease (Howeson et al., 1997), whereas other research suggests that more supported retrieval tests (e.g. recognition) are most effective (Small et al., 1997). In this study, both free recall and recognition of words were assessed on each measurement occasion in order to determine their relative importance in identifying persons at risk of developing Alzheimer’s disease. In addition, forward and backward digit spans were assessed to obtain preclinical measures of short-term memory performance.

Method

Subjects

The study sample consisted of all subjects who were non-demented after the first follow-up and participated in the second follow-up examination in the Kungsholmen Project. The Kungsholmen Project has been approved by the ethics committee of the Karolinska Institute in Stockholm, Sweden, and written informed consent was obtained from all participants after details of the procedure had been fully explained.

The original population included all inhabitants aged ≧75 years in the Kungsholmen parish of Stockholm (n = 1810). From this population, a subsample (n = 524) was selected to receive a comprehensive medical, social and cognitive assessment (Bäckman et al., 1994). Among the persons who participated in the comprehensive assessment, 189 had complete cognitive data and were non-demented at baseline and the first follow-up, which took place ~3 years later (mean 3.22 years, SD = 0.52). A description of the incident Alzheimer’s disease cases at the first follow-up is provided elsewhere (Small et al., 1997). During the 3-year interval (mean 3.51 years, SD = 0.44) between the first (Time 2) and second (Time 3) follow-up, 15 people were diagnosed with possible or probable Alzheimer’s disease, five were diagnosed with dementia of another type (e.g. vascular dementia, mixed dementia), 51 died, 10 moved or refused participation, one was eliminated because of a history of psychiatric disturbance, two were excluded because of a history of stroke, and 105 remained non-demented. The persons who developed Alzheimer’s disease and those who remained non-demented between Time 2 and Time 3 constituted the groups of interest in the present study.

The diagnosis of dementia and dementia type followed a three-step diagnostic procedure at each time of measurement. The presence of dementia and type of dementia was determined according to DSM-III-R criteria (American Psychiatric Association, 1987) with some modifications (Fratiglioni et al., 1992, 1997). First, a preliminary diagnosis was made by the examining physician. Secondly, all cases were reviewed by a specialized clinician, and a second preliminary diagnosis was made. In cases of agreement between the first and second diagnosis, this was the final diagnosis; in cases of disagreement, the final diagnosis was made by a supervising physician. Neuroimaging was not part of the diagnostic process. The cognitive data reported in this article were not used for diagnostic purposes.

Baseline (Time 1) background characteristics of the non-demented participants and incident Alzheimer’s disease cases at the second follow-up are presented in Table 1. A multivariate analysis of variance (MANOVA) revealed an overall effect of group status [Wilks λ = 0.892, F(4,115) = 3.49, P < 0.01]. Univariate analyses indicated that the incident Alzheimer’s disease group exhibited poorer global cognitive functioning, as indexed by the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) compared with
those who would remain non-demented [F (1,118) = 6.23, P < 0.05, \( \eta^2 = 0.05 \)]. There were no significant group differences (Ps > 0.05) in age, gender distribution, years of education or functional status (Katz et al., 1963).

**Measures of memory**

**Episodic memory**

Two tasks were used to assess episodic memory: free recall and recognition of words (Bäckman and Forsell, 1994). For free recall, two lists of 12 concrete nouns (e.g. child, pencil, horse, bicycle) were prepared. All nouns in the lists belonged to different taxonomic categories. The lists were comparable in terms of the length, concreteness and imagery of the nouns, as determined by a previous normative study (Molander, 1984). On each measurement occasion, approximately half of the participants received one list, whereas the other half received the other list. The specific list received varied among occasions. Participants were presented with the words at a rate of one word every 5 s. The presentation was bimodal: the words were shown on cards and the experimenter read them aloud simultaneously. Participants were instructed to remember as many words as possible for MANOVAs.

The outcomes from these MANCOVAs (multivariate analyses with the words at a rate of one word every 5 s. The presentation was bimodal: the words were shown on cards and the experimenter read them aloud simultaneously. Participants were instructed to remember as many words as possible for MANOVAs. The outcomes from these MANCOVAs (multivariate analyses of covariance) were similar to those from the MANOVAs. Therefore, in this article we focus on the results from the MANOVAs.

The second set of analyses examined the ability of the memory measures to predict who would develop Alzheimer’s disease. In this case, logistic regression analyses were conducted with diagnostic category (i.e. incident Alzheimer’s disease versus non-demented) as the outcome measure. After controlling for demographic factors, the four memory measures (free recall of words, recognition of words, digit span forwards, digit span backwards) were entered in stepwise fashion. The memory measures were converted into standard (Z) scores before analysis. Thus, the resulting odds ratios represent differences in risk per standard deviation unit rather than per raw score unit. Three logistic regression analyses were conducted. First, the Time 1 memory performance scores were used as predictors in the equation. Secondly, the predictive power of the memory measures from the second time of testing was examined. Thirdly, the utility of the Time 2 minus Time 1 difference scores as predictors

<table>
<thead>
<tr>
<th>Table 1  Baseline background characteristics of persons with incident Alzheimer’s disease and normal old persons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of Alzheimer’s disease 6 years later (Time 3)</td>
</tr>
<tr>
<td>Incident Alzheimer’s disease (n = 15)</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Per cent females</td>
</tr>
<tr>
<td>Years of education</td>
</tr>
<tr>
<td>MMSE(^{†})</td>
</tr>
<tr>
<td>ADL(^{‡})</td>
</tr>
</tbody>
</table>

Data are mean (standard deviation). \(^{*}P < 0.05.\) \(^{†}\)Mini-Mental State Examination (Folstein et al., 1975); \(^{‡}\)Katz ADL index (Katz et al., 1963).

Short-term memory

The Digit Span subtest of the Wechsler Adult Intelligence Scale—Revised (Wechsler, 1981) was used to index short-term memory. This test involved repeating a series of digits presented auditorily to the participant at the rate of 1 s per digit, according to standard procedures. Participants were asked to repeat the digits in forward and backward order.

Data analysis

The data analysis consisted of two main parts. First, we examined mean-level differences and longitudinal changes for the persons with incident Alzheimer’s disease and the non-demented persons. Specifically, we sought evidence for group differences both 6 and 3 years before diagnosis and examined whether the incident Alzheimer’s disease patients would exhibit a disproportionate decline in memory performance during the 3-year follow-up interval. Thus, three MANOVAs were conducted to investigate (i) group differences 6 years before diagnosis, (ii) group differences 3 years before diagnosis, and (iii) changes in memory performance during the 3-year follow-up period.

As noted, there was a group difference in MMSE performance at Time 1 favouring the non-demented persons (mean 28.07, SD = 1.61) over the incident Alzheimer’s disease cases (mean 26.93, SD = 1.91). This difference in MMSE score remained at Time 2 \([M_{ND} = 27.66, SD = 1.94; M_{IAD} = 25.67, SD = 2.87 (M = mean; ND = non-demented persons; IAD = persons with incident Alzheimer’s disease)].\) To determine whether the potential effects of preclinical Alzheimer’s disease on memory performance were independent of group differences in global cognitive functioning, we repeated the MANOVAs described below using the MMSE scores at Time 1 or Time 2 as covariates. The outcomes from these MANCOVAs (multivariate analyses of covariance) were similar to those from the MANOVAs. Therefore, in this article we focus on the results from the MANOVAs.
MANOVA conducted on the initial memory performance of Time 3 dementia status was determined. Because there was a large proportion of missing memory data in the incident Alzheimer’s disease group at the time of diagnosis, we were unable to include the third testing occasion in the analysis of these data.

Results

**Mean-level differences and changes**

Free recall and recognition data from the first and second times of measurement for the incident Alzheimer’s disease and normal old participants are presented in Fig. 1. A MANOVA conducted on the initial memory performance scores revealed a significant overall effect of diagnostic group [Wilks $\lambda = 0.831, F(4,115) = 5.86, P < 0.001$]. At the level of the individual variables, there were two reliable group differences: free recall [$F(1,118) = 15.64, P < 0.001$, $\eta^2 = 0.12$] and recognition [$F(1,118) = 10.69, P = 0.001$, $\eta^2 = 0.09$]. In both cases, the incident Alzheimer’s disease group performed worse than those individuals who would remain free of dementia. There were no group differences in either forward digit span ($M_{AD} = 5.13$, $SD = 0.99$; $M_{ND} = 5.67$, $SD = 1.12$) or backward digit span ($M_{AD} = 4.33$, $SD = 0.90$; $M_{ND} = 4.26$, $SD = 1.06$) ($P > 0.30$).

The MANOVA on the cognitive data for the 3-year follow-up (Time 2) revealed the same pattern of results, with an overall effect of group [Wilks $\lambda = 0.798, F(4,115) = 7.29$, $P < 0.001$], significant univariate differences for recall [$F(1,118) = 17.89, P < 0.001$, $\eta^2 = 0.13$] and recognition [$F(1,118) = 21.36, P < 0.001$, $\eta^2 = 0.16$], and no reliable differences for forward ($M_{AD} = 5.60$, $SD = 1.24$; $M_{ND} = 5.86$, $SD = 1.14$) or backward ($M_{AD} = 3.87$, $SD = 1.51$; $M_{ND} = 4.17$, $SD = 1.10$) digit span ($Ps > 0.30$).

Next, mean-level changes in memory performance from 6 years (Time 1) to 3 years (Time 2) before diagnosis were examined. Table 2 shows the mean-level changes expressed as $Z$-scores. A mixed MANOVA was conducted with group as the between-subjects factor and time as the repeated component. Consistent with the cross-sectional analyses, there was a significant overall effect for group [Wilks $\lambda = 0.769, F(4,115) = 8.64, P < 0.001$], with univariate differences in recall and recognition [recall: $F(1,118) = 22.01$, $P < 0.001$, $\eta^2 = 0.16$; recognition: $F(1,118) = 21.84$, $P < 0.001$, $\eta^2 = 0.16$]. There were no group differences for the digit span measures ($Ps > 0.30$). In addition, neither the main effect of time of testing nor the interaction between group and time was statistically significant ($Ps > 0.05$).

**Prediction of incident Alzheimer’s disease by memory performance**

To determine whether the lower episodic memory performance in preclinical cases of Alzheimer’s disease was independent of age, education and gender, logistic regression analyses were conducted. In these analyses, the demographic factors were entered first as covariates. The results from the logistic regressions are shown in Table 3. The first regression examined the predictive ability of the memory variables measured 6 years before diagnosis (Time 1). In this analysis, both recall and recognition contributed reliably to the model,

---

### Table 2 Changes in memory (Time 1 to Time 2) for persons with incident Alzheimer’s disease and normal old persons expressed as $Z$-scores

<table>
<thead>
<tr>
<th></th>
<th>Incident Alzheimer’s disease ($n = 15$)</th>
<th>Normal old persons ($n = 105$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free recall</td>
<td>$-0.26 (0.78)$</td>
<td>$-0.13 (0.99)$</td>
</tr>
<tr>
<td>Recognition</td>
<td>$-0.40 (1.19)$</td>
<td>$0.09 (1.04)$</td>
</tr>
<tr>
<td>Forward digit span</td>
<td>$0.41 (0.94)$</td>
<td>$0.16 (1.02)$</td>
</tr>
<tr>
<td>Backward digit span</td>
<td>$-0.42 (1.13)$</td>
<td>$-0.08 (0.98)$</td>
</tr>
</tbody>
</table>

Data are mean (standard deviation).

### Table 3 Logistic regression analyses for the prediction of dementia status 6 years (Time 1) and 3 years (Time 2) before diagnosis

<table>
<thead>
<tr>
<th>Time</th>
<th>Free recall</th>
<th>Recognition</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time 1</td>
<td>1.37</td>
<td>0.74</td>
<td>3.92</td>
<td>1.58–9.73</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>3.55</td>
<td>3.88</td>
<td>0.017</td>
<td>0.013–0.017</td>
<td></td>
</tr>
<tr>
<td>Time 2</td>
<td>1.15</td>
<td>0.69</td>
<td>3.15</td>
<td>1.28–7.76</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td>1.51</td>
<td>1.06</td>
<td>2.01</td>
<td>1.14–3.55</td>
<td>0.017</td>
</tr>
</tbody>
</table>

All effects are adjusted for age, education and gender.
whereas digit span was unrelated to the development of Alzheimer’s disease.

The second logistic regression model examined the predictive ability of the 3-year memory measures (Time 2). The results were strikingly similar to those of the previous analysis. Again, both recall and recognition made independent contributions, and the digit span measures did not contribute to the model.

The third regression model used the difference scores for the memory tests (Time 2 minus Time 1) as predictors. However, given that the mean-level analysis failed to demonstrate differential change for the incident Alzheimer’s disease group, thereby indicating approximately the same difference scores for the two groups, it is not surprising that the difference scores were unrelated to subsequent dementia status.

Discussion

The present results demonstrate impairment of episodic memory in the preclinical phase of Alzheimer’s disease >6 years prior to diagnosis (mean 6.73 years). This finding replicates and extends past observations (e.g. Fuld et al., 1990; Yoshitake et al., 1995; Fox et al., 1998). The marked episodic memory deficit among those who would develop Alzheimer’s disease can be contrasted with the complete absence of group differences in short-term memory, as indexed by the digit span test. The lack of group differences in backward digit span is especially noteworthy, given that this test requires temporal reorganization of digits, and thus poses demands on working memory (Baddeley, 1992). Deficits in working memory are routinely observed in early clinical Alzheimer’s disease (Baddeley et al., 1986; Morris, 1986). However, the present data suggest that such deficits may not be observed preclinically, at least when using backward digit span as the criterion test. This may reflect the fact that those prefrontal brain structures known to be critical to working memory functioning (Cabeza and Nyberg, 2000) are relatively little affected in the preclinical phase of Alzheimer’s disease (Braak and Braak, 1991).

The pattern of results obtained for episodic and short-term memory indicates that persons in a preclinical phase of Alzheimer’s disease have special difficulties in transferring information from a temporary to a more permanent representation, although the ability to hold information for a relatively brief period is well preserved (Bäckman and Small, 1998). There is converging evidence that the hippocampus and neighbouring regions are critical in establishing new episodic memory representations (Nyberg et al., 1996; Vargha-Khadem et al., 1997). Thus, it is conceivable that early changes in the hippocampal complex (Braak and Braak, 1995; Fox et al., 1996) play a major role in the episodic memory deficit observed in preclinical Alzheimer’s disease.

The finding that the normal old persons remained stable during the retest interval is consistent with the results from several longitudinal studies, indicating that decline in episodic memory may not be observed in normal ageing over relatively short follow-up periods (Hultsch et al., 1992; Zelinski et al., 1997). The most intriguing result in this study was that not only the control subjects but also the incident Alzheimer’s disease cases showed stability of episodic memory performance from 6 to 3 years prior to diagnosis. That is, although they already exhibited clear deficits in the episodic memory tests at the first time of measurement, the incident Alzheimer’s disease cases did not decline selectively between Time 1 and Time 2. In fact, the predictive accuracy for the memory variables was very similar at Time 1 and Time 2 (Table 3). As a result, the Time 2 minus Time 1 difference scores showed no predictive value in identifying those who would develop Alzheimer’s disease. Thus, the present data suggest that the episodic memory deficit in preclinical Alzheimer’s disease is characterized by an early onset followed by relative stability, at least until a few years before a diagnosis may be confirmed. Although a large amount of missing data in the incident Alzheimer’s disease group precluded an examination of memory performance at the time of diagnosis, several studies demonstrate precipitous episodic memory decline during the final portion of the preclinical phase in Alzheimer’s disease (Small et al., 1997; Fox et al., 1998; Rubin et al., 1998).

The fact that memory impairment may be observed >6 years before clinical diagnosis raises the issue of the actual onset of the preclinical phase of Alzheimer’s disease. Evidence from a study of nuns indicates that measures of linguistic skill assessed when participants were approximately 20 years of age were highly predictive of who would develop Alzheimer’s disease more than 50 years later (Snowdon et al., 1996). Related to this, histopathological data show that initial signs of the formation of neurofibrillary tangles (i.e. cytoskeletal changes) may already emerge in the trans-entorhinal cortex in early adulthood (Braak et al., 1993). Considering these observations together with those of the present study, it would appear that the neural changes eventually leading to clinical Alzheimer’s disease progress at a very slow rate, and that accelerated memory decline may not be expected until various biological processes (e.g. the formation of neurofibrillary tangles and amyloid plaques) have reached a certain threshold. Relevant to this argument are also recent findings that deleterious socioeconomic and environmental influences early in life may increase the risk of developing Alzheimer’s disease in late life (Hall et al., 2000; Moceri et al., 2000). Unfortunately, we lack data on cognitive performance for the present participants prior to their entry into the study. Thus, we are unable to address empirically the issue of a potential lifelong course of the preclinical phase of Alzheimer’s disease. However, as noted above, research suggests that this phase may start earlier in life than previously thought.

Another interesting observation was that tests of free recall and recognition alike were effective in discriminating between the two groups both 6 and 3 years before diagnosis. Several points should be made concerning the similar efficacy of
recall and recognition in identifying persons who would develop Alzheimer’s disease. First, there is some evidence that persons in a preclinical phase of the disease are characterized by losses in cognitive reserve capacity (Baltes et al., 1995) and, therefore, deficits may be particularly pronounced in tasks that offer some form of cognitive support, such as the retrieval support provided in a recognition test. Secondly, because recall is a more difficult test than recognition, the opposite argument could be made, namely that preclinical deficits should show up most clearly in tests of recall (Howieson et al., 1997). Obviously, our results do not support either of these contentions. Rather, the present findings suggest that the episodic memory impairment in preclinical Alzheimer’s disease generalizes across the two major tests of this form of memory.

A further point is that the incident Alzheimer’s disease cases, like the non-demented persons, performed at a much higher level in recognition than in recall both 6 and 3 years before diagnosis. Although it may be problematic to compare directly the present recall and recognition data because of differences in task difficulty, the qualitatively similar patterns of recall and recognition performance in the two groups should be highlighted (Fig. 1). This result indicates that persons in a preclinical phase of Alzheimer’s disease are able to use retrieval support to enhance memory, thus indicating a potential for memory improvement in this phase of the disease (Bäckman and Small, 1998). It has been argued that pharmacological treatment of Alzheimer’s disease-related memory deficits may profit by targeting persons at risk of developing Alzheimer’s disease rather than clinically verified cases (Petersen et al., 1999). Knowing that there is room for memory facilitation in preclinical Alzheimer’s disease should be useful, given this perspective on intervention.

**Acknowledgements**

This research was supported by grants from the Swedish Council for Research in the Humanities and the Social Sciences to Lars Bäckman, from the Swedish Medical Research Council to Laura Fratiglioni and from the Swedish Council for Social Research to Bengt Winblad, Lars Bäckman, and Laura Fratiglioni. We thank all members of the Kungsholmen Project study group for collaboration and data collection.

**References**


Accepted September 14, 2000