ORIGINAL INVESTIGATION

The Decreasing Prevalence of Reversible Dementias

An Updated Meta-analysis

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Background: In 1988, 2 meta-analyses suggested that the prevalence of reversible dementia was significantly lower than had been previously estimated. It was predicted that further work would indicate an even lower rate. The present study represents an updated meta-analysis of the true prevalence of reversible dementia.

Methods: MEDLINE was searched from 1987 through 2002. References were also gleaned from pertinent articles and relevant textbooks. Data were extracted on the nature and provenance of the studies, dementia etiology, and the proportion of cases that were potentially reversible and reversed.

Results: Fifty articles were identified of which 39 met the study criteria, representing 7042 patients of whom 5620 (87.2%) had dementia. Patients were classified according to etiology and, where possible (in 23 [59%] of 39 studies), whether the dementia partially or completely resolved. A much higher proportion of studies than was previously the case were either community-based (31%) or observed subjects from outpatient departments (54%). Alzheimer disease was still the commonest cause of dementia (56.3%) followed by a vascular etiology (20.3%). Conditions requiring neuroimaging made up only 2.2% of cases. Potentially reversible causes were seen in 9%, and only 0.6% of dementia cases actually reversed (0.29% partially, 0.31% fully).

Conclusions: The reported proportion of dementias that reverse is much lower than previously thought. While comorbidity should always be treated for its own sake and in the hope that cognitive decline may at least be delayed, the present findings have significant clinical and economic implications for the workup of dementia.

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In 1965, Adams et al[1] described reversal of dementia as a result of the surgical treatment of normal-pressure hydrocephalus (NPH). This discovery was the first in the field since the successful treatment of neurosyphilis in the 1940s.[2] During the 1970s and early 1980s, in part owing to increasing acceptance of the "geriatric ideology,"[3] additional studies were undertaken to further assess the possibility of reversibility. Very optimistic estimates were offered ranging from 10% to 40%.[4-9] However, skepticism based in part on the failure of most clinicians in the field to reproduce such findings led to a questioning of the view that dementia reversibility was so common.

In 1988, 2 separate meta-analyses[10,11] came to a similar conclusion, that is that reversibility actually occurred much less frequently than had previously been thought. In my earlier article,[11] a critical review of 32 studies conducted from 1972 through 1987, I found that of almost 3000 cases of dementia surveyed, at most only 11% reversed: 8% partially and 3% fully. Even at that time it was thought that the true incidence of reversibility was most probably lower than 11%.[10-12] This prediction was based on the presence of several biases and other factors inherent in the studies surveyed from those years.

A full description of this argument may be found in my earlier article,[11] but it can briefly be summarized as follows. First, patients studied in the 1970s and 1980s were younger (mean age, 72.3 years) than most patients presenting with dementia, and it was already known that dementias that do reverse were more likely to be found in younger patients and in those in whom the cognitive decline is more recent.[13] Second, referral filter bias[14] may well have been at work, since most studies done until 1987 originated from tertiary care inpatient settings. Only 4 (13%) of the 32 studies were community based[15-18] with adequate follow-up, and they described a lower

prevalence of reversibility than did the hospital-based research.

Finally, before 1988 it appears that little effort was made to use standardized instruments, to blind observers in determining improvement, to use a consensus approach to diagnosis, or to perform sufficient follow-up. As well, much of the improvement observed was only temporary, with the underlying dementia (usually caused by Alzheimer disease [AD], vascular disease, or mixed etiology) continuing to cause deterioration after an initial improvement.[6,12] In an attempt to investigate the hypothesis that the true prevalence of reversibility is indeed lower than had previously been reported, and to determine whether the rate of the reporting of reversibility has changed over the past decade and a half, I herein bring the 1988 meta-analysis[11] up to date.

METHODS

My methodology was similar to that used in the previous study,[11] although in the present analysis, I made a vigorous effort to meet the guidelines outlined by the MOOSE group (Meta-analysis of Observational Studies in Epidemiology).[19] A computer search from 1987 through 2002 was undertaken using the Index Medicus. (Although the previous study also included articles from 1987, the 5 included in the present review were not part of the previous analysis.) Key words included *dementia*, *dementia and etiology*, or *diagnosis*, or *differential diagnosis*, or *follow-up studies*, or *treatable dementias*, or *reversible dementias*, or *memory clinic*. As well, a follow-up of the relevant bibliography in articles identified by the electronic search was undertaken. Standard textbooks of geriatrics, neurology, internal medicine, and psychiatry were also consulted.

The rest of the methodology remained the same except in the calculation of the overall proportion of reversed (partial and full) dementia. In contrast to the previous analysis, where simple means were calculated, in this article I used the weighted average with inverse variance weights. For the sake of comparison, the reversibility data from the 1988 study were recalculated according to the weighted average method.

The search was restricted to English-language articles. All articles[20-58] that provided data according to the rubrics of **Table 1** (examining etiology) were included. Those that addressed the issue but from which the data could not be extracted to fit Table 1 were excluded.[59-69] For example, if the total number of patients with dementia did not correspond to the sum of the individual etiologies or if it was not possible to understand the etiologic definition, the study was excluded.

In certain cases, I clarified issues through correspondence with the authors of the articles. Where the information received was relevant it was included; such has been noted in the tables.

RESULTS

The results of the present study are represented in a format similar to that of my earlier meta-analysis[11] (Table 1, **Table 2**, and **Table 3**). (For comparative purposes, the information in brackets below applies to the data from the 1972-1987 study.[11]) In total, of the 50 articles reviewed in the present study, 39 [32] relevant studies published between 1987 and 2001 were further examined (Table 2). The mean sample size of the studies included was 168.2 [82.5] for a total of 5620 [2889] patients with dementia. The mean age of the patients was 74.4 years [72.3 years], and in contrast to the previous survey [41%], almost all of the studies surveyed here (36/39; 92%) reported the specific age of the subjects. The remaining 3 offered more general age data such as "all patients 65 years or older." Many fewer studies in the present analysis originated in tertiary care centers, and the percentage that examined inpatient populations fell from [67%] in 1988 to only 15% in the present analysis. None [7%] used subjects from long-term care institutions, and the proportion of those studies based on community samples rose from [13%] to 31% (**Table 4**).

The reported etiologies are indicated in Table 1. Alzheimer disease was still the commonest cause, involving 56.3% [56.8%] of cases, followed by a vascular etiology at 20.3% [13.3%]. The rest of the breakdown was more or less similar to that in the previous study except for a fall in the prevalence of medication as a cause, from [1.5%] to 0.1% and depression from [4.5%] to 0.9%. In the present study, the percentage of the total assessed defined as not demented was much higher than the figure reported in the earlier analysis (18.7% vs [3.7%]). A full comparison of the distribution of different etiologies of dementia between the 2 studies can be found in **Table 5**.

Table 3 offers a breakdown of the number of reversible cases of dementia, indicating that 355 (9%) were potentially reversible compared with [13.2%] in the earlier study.[11] Follow-up information enabling the reader to determine whether the potentially reversible cases actually improved after treatment of the underlying cause was provided more often in the presently analyzed studies than in those reviewed earlier, that is in 23 (59%) of 39 studies [36%]. In those articles where follow-up was provided, only 0.29% (confidence interval, 0.09%-0.48%) [8%] of cases reversed partially, and 0.31% (confidence interval, 0.12%-0.5%) [3%] reversed completely, for a total of 0.6% (confidence interval, 0.33%-0.87%) [11%] reversibility.

The data from my earlier analysis[11] were recalculated with the same methods used for the present review (Table 4). It is of interest that with the newer method, the 1988 figures for reversibility fall somewhat but are still much higher than was found in the present analysis.

COMMENT

REASONS FOR A DECREASE IN THE PREVALENCE OF REVERSED DEMENTIA

Better Recent Methodology

As predicted, the more recent data from studies for the years 1987 through 2002 indicate that the reported prevalence of reversibility (potential, partial, and full) has indeed fallen compared with that described in the earlier meta-analysis,[11] from a total of [11%] to less than 1%. What can explain these differences? First, let us examine the initial possibilities outlined in the previous article.[11]

The patients in the present analysis are older (mean age, 74.4 years), somewhat closer to the age of patients with dementia in the community. It is known that the

Table 1. Dementia Etiology*

Source	AD	VaD	Mixed	Infectious	Metabolic	Tumor	NPH	SDH	Depression	Meds
Bayer et al,[20] 1987	40	9	5			2[a]			13	
Erkinjuntti et al,[21] 1987	73	70	5			8	3	2	4	
Hedner et al,[22] 1987	21	35	9		1		1			
Philpot and Levy,[23] 1987	42	8								
Van der Cammen et al,[24] 1987	25	3								1
Thal et al,[25] 1988	264	18	34		5	3	2			
Brayne and Calloway,[26] 1989	15	9	1							
Evans et al,[27] 1989	103	3							1	
Katzman et al,[28] 1989	32		15[b]		3	1	1			
Brodaty et al,[29] 1990	77	16	9						[12][c]	
Cunha et al,[30] 1990	?[d]	18			19	1	2		4	
Livingston et al,[31] 1990	22	1	5			1				
Roberts and Caird,[32] 1990	124	79		3	3	22	5	10		1
Zhang et al,[33] 1990[f]	103	43								
Folstein et al,[34] 1991	12	7	3				1			
Liu HC et al,[35] 1991	40	43	3			7	2	2		
Varga et al,[36] 1991	68	26	23			2	3		1	
Ames et al,[37] 1992	50	21								
Liu CK et al,[38] 1992	23	30	12	3		2	2			
McMurdo et al,[39] 1993	26	5			1				8	2
Skoog et al,[40] 1993	64	51	12		1		1	1		
Ebly et al,[41] 1994	388	69								
Nitrini et al,[42] 1995	54	20		4			6[g]			
Swanwick et al,[43] 1996	101	16	20							
White et al,[44] 1996	77	68	53		1			2		
Auchus et al,[45] 1997	33[h]	6[i]	9	1	[2]		1		3[j]	
Chui and Zhang,[46] 1997	53[k]	17	26			1			2	
Kua et al,[47] 1997	25	20								
Walstra et al,[48] 1997	114	1	13		26					
Freter et al,[49] 1998	127	5	18		10[l]	2[l]	4[l]		23[l]	10[l]
Liu CK et al,[50] 1998	25	19	9		1					
Ogunniyi et al,[51] 1998	40	14	12	3			2			
Andreasen et al,[52] 1999	220	200	19							
Farina et al,[53] 1999	260	29		1	3	1	5		14	
Hogh et al,[54] 1999	74	28	12				19			
Sahadevan et al,[55] 1999	40	55				1	1		2	
Von Strauss et al,[56] 1999	274	64								
Burke et al,[57] 2000[m]	17	14	6							
Massoud et al,[58] 2000	29[o]	0	18							
Total	**3171** (56.4)	**1140** (20.3)	**351** (6.2)	**15** (0.3)	**64** (1.1)	**53** (0.9)	**57** (1.0)	**17** (0.3)	**52** (0.9)	**4** (0.1)

Source	Trauma	Anoxic	Huntington Disease	Parkinson Disease	Alcohol	Misc	Demented	Not Demented	Total Assessed
Bayer et al,[20] 1987				4	5		78	22	**100**
Erkinjuntti et al,[21] 1987	2		1	5	4	11	188	135	**323**
Hedner et al,[22] 1987						2	69	6	**75**
Philpot and Levy,[23] 1987						1	51	49	**100**
Van der Cammen et al,[24] 1987						4	33	17	**50**
Thal et al,[25] 1988						10	336	39	**375**
Brayne and Calloway,[26] 1989						4	29	0	**29**
Evans et al,[27] 1989				1	2		110	3	**113**
Katzman et al,[28] 1989					2	2	56	0	**56**
Brodaty et al,[29] 1990				1	[2][c]	3	106	38	**144**
Cunha et al,[30] 1990						66[d]	110	0	**110**
Livingston et al,[31] 1990				2	1	11	43	5	**48**
Roberts and Caird,[32] 1990			1		4[e]	12	264	16	**280**
Zhang et al,[33] 1990[f]						13	159	0	**159**
Folstein et al,[34] 1991							22	10[f]	**32**
Liu HC et al,[35] 1991	1	2		5	1	4	110	21	**131**
Varga et al,[36] 1991	1	3	1	25	3	13	169	6	**175**
Ames et al,[37] 1992	1				2		74	26	**100**
Liu CK et al,[38] 1992				5		9	86	14	**100**
McMurdo et al,[39] 1993	1				1	3	47	3	**50**
Skoog et al,[40] 1993		6			4	7	147	0	**147**

(continued)

Table 1. Dementia Etiology* (cont)

Source	Trauma	Anoxic	Huntington Disease	Parkinson Disease	Alcohol	Misc	Demented	Not Demented	Total Assessed
Ebly et al,[41] 1994						58	515	0	**515**
Nitrini et al,[42] 1995				8	1	7	100	0	**100**
Swanwick et al,[43] 1996						50	187	13	**200**
White et al,[44] 1996	2			12		11	226	200	**426**
Auchus et al,[45] 1997	1			1	[1]	3	58	0	**58**
Chui and Zhang,[46] 1997	1	1		4		5	110	9	**119**
Kua et al,[47] 1997							45	27	**72**
Walstra et al,[48] 1997	1			1		13	169	30	**199**
Freter et al,[49] 1998				2	1[l]		196	109	**305**
Liu CK et al,[50] 1998	2			2		2	60	0	**60**
Ogunniyi et al,[51] 1998				6			77	7	**84**
Andreasen et al,[52] 1999						50	489	130	**619**
Farina et al,[53] 1999						47	362	151	**513**
Hogh et al,[54] 1999						50	183	217	**400**
Sahadevan et al,[55] 1999				1			100	0	**100**
Von Strauss et al,[56] 1999				4	6	10	358	0	**358**
Burke et al,[57] 2000[m]							37	19[n]	**56**
Massoud et al,[58] 2000						14	61	0	**61**
Total	**13** (0.2)	**12** (0.2)	**3** (0.1)	**89** (1.6)	**36** (0.6)	**429** (7.6)	**5620** (100.0)	**1322**	**7042**

Abbreviations: AD, Alzheimer disease; Meds, medications; Misc, miscellaneous; NPH, normal-pressure hydrocephalus; SDH, subdural hematoma; VaD, vascular dementia.

*Numbers in brackets refer to causes that are included in other primary etiologies, and thus not in the totals. [a]Both "inoperable"; [b]vascular and mixed; [c]included in 38 "not demented"; [d]of 66 "miscellaneous," probably a good portion were AD; [e]alcohol/trauma; [f]includes 5 "not demented" and 5 "possible dementia"; [g]includes 2 with "hypertensive hydrocephalus"; [h]includes 25 "probable dementia": 4 possible AD and alcohol abuse, 3 possible AD and "dementia syndrome of depression"; [i]includes 4 "probable VaD": 1 possible VaD and "dementia syndrome of depression, 1 possible VaD and hydrocephalus; [j]includes 2 "dementia syndrome of depression," 1 "dementia syndrome of depression and B_{12} deficiency"; [k]includes 4 "possible AD"; [l]these 50 conditions occurred in 45 patients; [m]diagnoses at 1-year follow-up of 80 initially assessed; [n]includes 9 with "no diagnosis," 3 with "amnestic disorder," and 7 with "mild neurocognitive disorder"; [o]includes 2 with B_{12} deficiency, 3 with hypothyroidism, 2 with hyperthyroidism, and 2 with positive VDRL. None of these 9 patients reversed on treatment.

likelihood of AD and vascular disease, both irreversible causes of dementia, increases with age.[27,40]

As well, it seems that both earlier research[13] and more recent studies[21,32,35,53,69] support the notion that reversed or potentially reversible causes tend to be seen in relatively young patients or in those with a more recent onset of symptoms. This notion is supported by Farina et al,[53] who found that no cases of "severe" dementia had a reversible cause. In addition, the percentage of affected women has risen, further pushing the profile of the study sample closer to that of the typical population with dementia.

Especially important is the fact that there are so many more outpatient and community-based studies in the present meta-analysis. The community studies* indicate that when the selection bias observed in hospital-based research is eliminated, the proportion of AD as a cause of dementia markedly increases. For example, Evans et al[27] in their analysis of the East Boston sample found that of those with moderate or severe cognitive impairment in the community, 84.1% had clinically diagnosed AD as the most probable cause.

In the 9 (75%) of 12 community-based studies that reported such data,[26-28,31,33,40,45,50,56] dementia from potentially reversible causes accounts for just over 4% of cases. Even in the unlikely case that in all of these patients the dementia fully reversed and did not exhibit any recrudescence of cognitive decline, 4% is just over one third of the figure of [11%] generated in 1988[11] for the total that actually were seen to reverse. For those 5 community-based studies[28,31,41,50,56] that reported reversibility (Table 3), the prevalence of reversibility falls to almost to 0 (1/1032).

Given the increase in the proportion of community-based studies, referral filter bias may explain a good part of the variance. Weytingh et al[70] propose that the prevalence of reversibility has fallen in large part because of a change from inpatient to outpatient settings and the more recent use of stricter assessment methods that use a multidisciplinary approach.[62] Evaluation of research published between 1975 and 1992 can provide insight into this argument.* Others concur with this analysis.[79]

As well, Weytingh et al[70] suggest that an improvement in diagnostic assessment in general practice may have contributed to the lower proportion of patients with reversible dementia being referred to the studies surveyed in the present review. Indirect evidence in support of this trend may be adduced by the finding in the present survey that medication as a cause of dementia is now very rarely reported (0.1% now compared with [1.5%] of dementias in the earlier study[11]). It may well be that many primary care physicians have taken the principles of geriatric pharmacology to heart and are being more conservative or at least more vigilant with respect to the adverse effects of medication on cognition.

Evidence for more careful attention to standardized instruments can be found when one compares the previous and present proportions of those deemed not de-

References 26-28, 31, 33, 34, 40, 41, 45, 50, 52, 56.

References 12, 13, 20, 22, 29-31, 37, 71-78.

Table 2. Sample Size, Patient Demographics, and Sample Provenance Data

Source	Sample Size (Demented) (N = 5620)	Study Design	Age, y*	Female, %	Patient Setting	Origin Department	Country
Bayer et al,[20] 1987	75	R	74.2 (50-89)	47	OPD	Geriatrics	UK
Erkinjuntti et al,[21] 1987	188	P	64.9 ± 0.8	54.5	OPD, 80.5%/IPD, 19.5%	Neurology	Finland
Hedner et al,[22] 1987	69	P	84 (69-97)	73.3	IPD	Psychogeriatrics	Sweden
Philpot and Levy,[23] 1987	51	P	M: 68.7, F: 66.0	74	OPD	Psychogeriatrics	UK
Van der Cammen et al,[24] 1987	33	P	75.2 (61-90)	64	OPD	Geriatrics	UK
Thal et al,[25] 1988	336	P	68.7 ± 0.5	20	OPD	Neurology	US
Brayne and Calloway,[26] 1989	29	P	70-79	100	C	Epidemiology	UK
Evans et al,[27] 1989	110	P	≥65	?	C	Medicine/neurology	US
Katzman et al,[28] 1989	56	P	≥79	64.5	C	Neurology/geriatrics	US
Brodaty,[29] 1990	106	R	71.9 ± 8 (44-88)	65	OPD	Psychogeriatrics	Australia
Cunha,[30] 1990	110	P	76.2 (60-92)	63	OPD	Geriatrics	Brazil
Livingston et al,[31] 1990	43	P	80 (65-93)	77	C	Geriatrics	UK
Roberts and Caird,[32] 1990	264	R	73.5	65.4	IPD	Neurology/geriatrics	UK
Zhang et al,[33] 1990	159	P	≥55	56.3	C	Epidemiology	China
Folstein et al,[34] 1991	32	P	65-92	48.8	C	Psychiatry	US
Liu HC et al,[35] 1991	110	P	67.9 ± 9 (37-87)	19.1	OPD/IPD	Neurology	Taiwan
Varga et al,[36] 1991	169	R	71.4 (20?-92)	44.2	IPD	Neurology	Canada
Ames et al,[37] 1992	74	P	75.5 ± 6.9 (54-90)	75	OPD	Geriatrics	Australia
Liu CK et al,[38] 1992	86	P	67.1 ± 10.8 (28-88)	41.8	IPD	Neurology	Taiwan
McMurdo et al,[39] 1993	50	P	71 (56-88)	68	OPD	Geriatrics	Scotland
Skoog et al,[40] 1993	147	P	≥85	75	C	Geriatrics	Sweden
Ebly et al,[41] 1994	515	P	88.3 ± 3.3	78.3	C	Pathology/neurology/ medicine	Canada
Nitrini et al,[42] 1995	100	P	67.6 ± 11.7	39	OPD	Neurology	Brazil
Swanwick et al,[43] 1996	187	P	74.3 ± 6.1 (58-92)	71.5	OPD	Geriatrics/psychiatry	Ireland
White et al,[44] 1996	226	P	78 (71-93)	0	C	Epidemiology	US (Hawaii)
Auchus et al,[45] 1997	58	R	74.6 ± 6.5	76	OPD	Neurology/geriatrics	US (blacks only)
Chui and Zhang,[46] 1997	110	R	69.9 ± 8.4	65	OPD	Neurology	US
Kua et al,[47] 1997	45	P	73.3	55.5	OPD	Psychiatry	Singapore
Walstra et al,[48] 1997	169	P	79.2 ± 6.3	60	OPD	Neurology	Holland
Freter et al,[49] 1998	196	R	74.6 (49-92)	55.6	OPD	Geriatrics	Canada
Liu CK et al,[50] 1998	60	P	75.8	51.6	C	Neurology	Taiwan
Ogunniyi et al,[51] 1998	77	R	74.6 ± 11.8 (50-98)	36.4	IPD	Neurology	Saudi Arabia
Andreasen et al,[52] 1999	489	P	77.4 ± 7.3	59.9	C	Rehab/geriatrics	Sweden
Farina et al,[53] 1999	362	R	71.6 ± 8.9	55.2	OPD	Neurology	Italy
Hogh et al,[54] 1999	183	P	63.6	47.5	OPD	Neurology	Denmark
Sahadevan et al,[55] 1999	100	R	79.5†	56	IPD	Geriatrics	Singapore
Von Strauss et al,[56] 1999	358	P	88.6 ± 5 (78-102)	85.2	C	Geriatrics/psychiatry	Sweden
Burke et al,[57] 2000	37	P	70 ± 9.7	53.8	OPD	Geriatrics	Australia
Massoud et al,[58] 2000	61	P	69 ± 11	41	OPD	Neurology/psychiatry	US

Abbreviations: C, community based; IPD, inpatient department; OPD, outpatient department; P, prospective; R, retrospective.
*Given as a mean, mean (range), range, or mean ± SD, depending on information available. Mean age of all studies is 74.4 years.
†Estimated from Table 2 of Sahadevan et al.[55(p268)]

mented (see Tables 1 and 5). While this figure was only [3.7%] in the 1988 meta-analysis,[11] in the present review this percentage has increased to 18.6%, suggesting that the authors of the recent studies have been more careful and consistent in their diagnosis of what constitutes dementia.

Further support for the hypothesis that more careful and standardized assessment results in the reporting of lower prevalence rates of reversibility can be found in Walstra et al.[48] Although complete reversal was seen in none of the 169 patients assessed in a memory clinic, on clinical impression alone, 5 patients had initially appeared to improve after treatment of a potentially reversible cause. However, "measured assessment did not confirm this [putative improvement]."[48(p20)]

Weytingh et al[70] solicited referral from general practitioners in their catchment area who were systematically encouraged to refer all patients with cognitive impairment, thus discouraging any "leakage" of reversible cases before referral. Despite this care, the prevalence of reversed dementia was extremely low.

Depression

The lower numbers may also be explained in part by the better and more consistent follow-up offered in more recent studies. For example, careful attention to the durability of dementia improvement with treatment of the underlying cause seems to have further uncovered a phenomenon that was first noted with the cognitive decline associated with depression. In 1984, Reding and colleagues[80] found that on follow-up, of the 15 patients in a specialized dementia clinic initially diagnosed with depression and treated appropriately, more than half manifested progressive intellectual impairment.

Table 3. Patients With Potentially Reversible, Partly Reversed, and Fully Reversed Dementia

Source	No. in Study	No. (%) of Patients				
		Total Demented (N = 5620)	Potentially Reversible Disease	Partially Reversed Disease	Fully Reversed Disease	Total Reversed Disease
Bayer et al,[20] 1987	100	78	27	0	0	0
Erkinjuntti et al,[21] 1987	323	188	19	NR	NR	NR
Hedner et al,[22] 1987	75	69	2	0	1	1
Philpot and Levy,[23] 1987	100	51	0	0	0	0
Van der Cammen et al,[24] 1987	50	33	1	1	0	1
Thal et al,[25] 1988	375	336	13	1	4	5
Brayne and Calloway,[26] 1989	365?	29	4[a]	NR	NR	NR
Evans et al,[27] 1989	113	110	3	NR	NR	NR
Katzman et al,[28] 1989	56	56	7	0	0	0
Brodaty et al,[29] 1990	144	106	0	0	0	0
Cunha et al,[30] 1990	110	110	26	0	2[b]	2
Livingston et al,[31] 1990	48	43	2	0	0	0
Roberts and Caird,[32] 1990	280	264	48	NR	NR	NR
Zhang et al,[33] 1990[f]	159	159	13[c]	NR	NR	NR
Folstein et al,[34] 1991	32	22	NR	NR	NR	NR
Liu HC et al,[35] 1991	131	110	12	NR	NR	NR
Varga et al,[36] 1991	175	169	9	NR	NR	NR
Ames et al,[37] 1992	100	74	6	0	0	0
Liu CK et al,[38] 1992	100	86	7	4	1	5
McMurdo et al,[39] 1993	50	47	4	NR	NR	NR
Skoog et al,[40] 1993	147	147	8	NR	NR	NR
Ebly et al,[41] 1994	515	515	NR	0[d]	0[d]	0[d]
Nitrini et al,[42] 1995	100	100	8	5	2	7
Swanwick et al,[43] 1996	200	187	NR	NR	NR	NR
White et al,[44] 1996	426	226	3	NR	NR	NR
Auchus et al,[45] 1997	58	58	NR	NR	NR	NR
Chui and Zhang,[46] 1997	119	110	3	NR	NR	NR
Kua et al,[47] 1997	72	45	0	0	0	0
Walstra et al,[48] 1997	199	169	33	1	0	1
Freter et al,[49] 1998	305	196	45	4	3	7
Liu CK et al,[50] 1998	60	60	1	0[e]	1[e]	1[e]
Ogunniyi et al,[51] 1998	84	77	3	2	0	2
Andreasen et al,[52] 1999	619	489	NR	NR	NR	NR
Farina et al,[53] 1999	513	362	26	5	13	18
Hogh et al,[54] 1999	400	183	19	NR	NR	NR
Sahadevan et al,[55] 1999	100	100	4	1[f]	2[f]	3[f]
Von Strauss et al,[56] 1999	358	358	6	0[g]	0[g]	0[g]
Burke et al,[57] 2000[m]	56	37	1	1[h]	0	1[h]
Massoud et al,[58] 2000	61	61	9	0	0	0
Mean, %			9[i] (355/3940)	0.29[j] (CI, 0.09-0.48)	0.31[j] (CI, 0.12-0.5)	0.6[j] (CI, 0.33-0.87)

Abbreviations: CI, confidence interval; NR, not reported.

[a]Assuming all 4 "secondary dementias" were potentially reversible, of those reported. [b]Personal communication, U. Cunha.[30] [c]Assuming all 13 "others" were potentially reversible. [d]Personal communication, D. Hogan.[41] [e]Personal communication, C. K. Liu.[50] [f]The 1 patient with normal-pressure hydrocephalus showed "only marginal improvement" (personal communication, S. Sahadevan[55]). [g]Personal communication, E. von Strauss.[56] [h]"Mild cognitive disorder" both initially and after 1 year of follow-up (Burke et al[57]). [i]For 33 studies reporting. [j]For 23 studies reporting.

More recently, Alexopoulos et al[81] reported similar findings in a longitudinal investigation designed to calculate the rate of development of "irreversible" dementias in elderly depressed patients that reversed after treatment and subsequent improvement of the cognitive decline. They found that irreversible dementia developed more frequently in the depressed group with "reversible" cognitive decline than in the group with depression alone.

A population-based longitudinal study of dementia in Stockholm[82] reported that the depressive symptoms are often evident preclinically in Alzheimer disease. Furthermore, these symptoms are not simply a by-product of self-perceived cognitive difficulties.

These findings and those of others[83,84] suggest that the treatment of depression early in the course of dementia may be helpful with respect to cognition, at least early on. However, any initial cognitive improvement may be misinterpreted as reversibility, especially if sufficient follow-up is not undertaken.

Metabolic Etiologies

Other conditions were also seen on follow-up to act in a manner analogous to depression. For example, a rigorous analysis of 2781 cases of hypothyroidism[85] found only 1 case of reversible dementia secondary to hypothyroidism. Dugbartey[86] came to a similar conclusion.

Table 4. Comparison of the 2 Study Periods

	1972-1987	1987-2001
No. of studies	32	39
No. of patients	2889	7042
No. with dementia	2781	5620
Age, mean, y	72.3	74.4
Female, %	47.9	58.1
Setting, No. (%)		
IPD	20/30 (67)	6/39 (15)
OPD	5/30 (17)	21/39 (54)
Community	4/30 (13)	12/39 (31)
Nursing home	2/30 (7)	0
Reversibility, %		
Potential	13.2	9.0
Partial (a)		
Not weighted*	8	. . .
Weighted†	3.7	0.3 (CI, 0.09-0.48)
Full (b)		
Not weighted	3	. . .
Weighted	1.3	0.3 (CI, 0.12-0.50)
Total (a + b)		
Not weighted	11	. . .
Weighted	7.0	0.6 (CI, 0.33-0.87)

Abbreviations: CI, confidence interval; IPD, inpatient department; OPD, outpatient department.
*Simple mean.
†Weighted mean calculated according to inverse variance weights method.

Table 5. Comparison of Dementia Etiology Between Present Study and 1988 Analysis*

	1972-1987	1987-2001
Etiology, %		
AD	56.8	56.3
VaD	13.3	20.3
Mixed	0.8	6.2
Infectious	0.6	0.3
Metabolic	1.5	1.1
Tumor	1.5	0.9
NPH	1.6	1.0
SDH	0.4	0.3
Depression	4.5	0.9
Meds	1.5	0.1
Trauma	0.4	0.2
Anoxic	0.2	0.2
Huntington disease	0.9	0.1
Parkinson disease	1.2	1.6
Alcohol	4.2	0.6
Misc	6.9	7.6
Demented, No.	2781	5620
Not demented, No.	108	1322
Total assessed, No.	2889	7042
Not demented/total assessed, %	3.7	18.8

Abbreviations: AD, Alzheimer disease; Meds, medications; Misc, miscellaneous; NPH, normal-pressure hydrocephalus; SDH, subdural hematoma; VaD, vascular dementia.
*Percentages derived in present study (1987-2001) use number of "demented" as denominator. In the 1988 study (1972-1987) the "total assessed" constituted the denominator.

Another classic reversible etiology, vitamin B_{12} deficiency, has been well known to cause a host of neurologic deficits including cognitive impairment since the first description of the disease by Addison in 1858.[87] For example, Cunha et al[88] examined B_{12} deficiency (<200 pg/mL) in 46 (25%) of 181 outpatients with dementia. Unfortunately, despite adequate cyanocobalamin (vitamin B_{12}) replacement, over 84% of those treated manifested persistent cognitive decline over a 3- to 24-month follow-up. Those few patients who did improve had a mild dementia with a relatively recent onset (<2 years). Others have reported similar results.[22,89,90]

A report from the Bronx Longitudinal Aging Study[91] examined the problem from the opposite direction and found that the B_{12} deficiency may well be secondary in many cases to the dementia and not its cause.[92,93]

Intracerebral Etiologies and the Use of Neuroimaging

The reversibility hypothesis was initiated or at least rejuvenated by the publication in 1965 of the classic article by Adams et al[1] on NPH, a condition that today requires neuroimaging for diagnostic confirmation. Two other potential causes of dementia, subdural hematoma and cerebral tumors, also require such confirmatory testing. In the 1988 study,[11] these 3 conditions made up only [3.5%] of all dementias, and in the present analysis that number has fallen to 2.2%. As well, there is much debate, especially with respect to NPH, regarding the efficacy of surgical intervention[94] and, by extension, the need for a universal recommendation for neuroimaging.[95,96]

With respect to the incidence of clinically important subdural hematoma, NPH, and intracranial tumor in a population-based study, Alexander et al[97] found only 145 such lesions identified among 137 100 person-years at risk. They concluded that such lesions are rare and that "Most cases have presentations that easily distinguish them from typical Alzheimer's disease."[97(p138)]

Several studies have examined the efficacy of neuroimaging in the dementia workup. For example, Walstra et al[48] pointed out in their memory clinic population that "CT [computed tomography] never influenced diagnosis or management."[48(p20)]

Freter et al[49] also studied the issue by retrospectively testing the CT clinical guidelines generated by the first Canadian Consensus Conference on the Assessment of Dementia (CCCAD) held in 1989[98] and ratified in the second meeting of this group in 1998.[99] These guidelines were found to be quite robust in their analysis. Had the CCCAD recommendations been followed, neuroimaging would only have been used in 38.8% of the 196 dementia cases assessed in this memory clinic. More to the point, only 1 of 6 patients with a lesion would have been "missed" (a patient with a glioma who did not improve after neurosurgery and died within a year of diagnosis).

Other authors, such as Farina et al[53] and Engel and Gelber,[100] found the CT scan to be of use only in patients exhibiting either neurologic signs or an atypical dementia. Others concur.[36,58]

Foster et al[101] offer a systematic review of the use of CT scanning in dementia via construction of a model based on the 1988 meta-analysis[11] as well as 4 other relevant studies[102-105] involving more than 4800 patients. While the authors conclude that CT scanning is probably cost-effective in the rare patient younger than 65 years who presents with dementia, for elderly patients, who com-

prise the bulk of patients with dementia seen in practice, the researchers suggest a selective use of CT. As well, Flaherty and Hoskinson[106] warn of the emotional distress that can be engendered in elderly patients with dementia when they undergo magnetic resonance imaging.

In an interdisciplinary clinic, Chui et al[46] studied the outcome of using the 1994 American Academy of Neurology guidelines, which then recommended a selective approach.[107] They found, as did Freter et al[49] a year later, a tolerable false-negative rate (5%) and an acceptable false-positive rate (36%). However, referring to these same data, in 2001 the American Academy of Neurology changed their recommendation to a near-universal neuroimaging policy.[108]

The argument has been made that the use of tests is simply a question of resources and that in either a public system (if resources were available) or a private system (if the patient were willing to pay) there would be no harm in a comprehensive, universal testing strategy. Yet as Black and Welch[109] have pointed out with respect to the benefits to therapy of recent advances in diagnostic testing, "[U]nfortunately, these technological advances also create confusion that may ultimately be harmful to patients."[109(p1237)]

It has been argued that too vigorous a search for these 3 conditions (subdural hematoma, cerebral tumors, and especially NPH) may well do more harm than good in a population of elderly patients with dementia.[94,95] That being said, interventionist views are not uncommon, often supported by authoritative articles. A good example, but one that unfortunately is based on outdated figures, can be found in an article on neuroimaging published several years ago in the *New England Journal of Medicine*. Therein, Gilman[110] stated (without citation) that "up to 30 percent of patients with dementia have a reversible disorder, including drug effects, metabolic disorders, stroke, vitamin deficiencies, and depression ('pseudodementia')."[110(p894)]

But this is indeed a controversial issue. There is a school of thought, articulated by George et al,[111] Katzman,[96] and in the recent guidelines of the American Academy of Neurology,[108] that calls for a universal or near-universal scanning policy. For a balanced approach relating to the various clinical guidelines that address the issue, see the excellent recent review by Gifford et al.[112] An analogous critique of preoperative laboratory testing has recently been offered by Roizen.[113]

PROGNOSTIC FACTORS FOR REVERSIBILITY

Despite the low overall prevalence of reversibility, it still does exist in patients who have not yet deteriorated enough to be formally labeled as *demented*: the young, the newly symptomatic, and those whose complaints are still mild (mild cognitive impairment). There is also biological plausibility to this hypothesis. A certain proportion of those patients with dementia from potentially reversible causes surveyed in the present meta-analysis may not have improved because treatment of the underlying disease was not started early enough. And there is often a significant lag, both for dementia in general[114] and for AD in particular,[115] between the first signs of dementia and a definitive diagnosis. In support of this theory, Draper[116] has found that cognitively impaired patients without dementia tend to have a better prognosis. Similar findings have been reported for vitamin B_{12} deficiency.[90]

An alternative explanation may be simply that the prevalence of AD, and that of many other potentially reversible etiologies, increases with age. Thus it should not come as a surprise that 2 (or more) diseases can coexist, especially in an elderly individual, with neither causing the other.

METHODOLOGIC PROBLEMS AND BIASES IN THE PRESENT STUDY

The potential biases inherent in the studies surveyed have been addressed above, but what of the methodologic problems involved in the process of meta-analysis.[117] Publication bias[118,119] may exist, although what constitutes a negative or positive survey of dementia etiology remains questionable. However, in many of the studies published, the goal of the authors (either explicitly or implicitly) was to indicate that reversibility exists, so if there were any bias in these studies it would work in most cases to raise the prevalence of reversibility rather than lower it. Thus, the figures presented here are likely to constitute, if anything, an overestimate of reversibility's true prevalence.

Data excess, as described by Naylor,[117] does not appear to be in evidence either in the present analysis or in my earlier effort.[11] In neither analysis is there evidence of duplicate publication.

With respect to the potential for meta-analyses to conflict with one another, the results of the present update and the original meta-analysis[11] are coincident with the findings of the only other 2 relevant works identified,[10,70] despite the differences in methods and years surveyed.

Publication bias involving language may well be at work here in that only literature published in English was included. However, this is unlikely to constitute a serious problem because of the 39 articles surveyed here, 17 different countries are represented, in almost half of which English is not the mother tongue.

A technical consideration also influences and somewhat narrows the gap between the 1988 figures[11] and those in the present study. In the first meta-analysis,[11] the method of simple computation of means was used without weighting. However, after recalculating the reversibility figures from the 1988 study using the same weighted mean method used in the present survey, I found the total reversibility to be 7% rather than the [11%] originally reported (change in partial reversal, [8%] to 3.7%; full reversal, [3%] to 1.3%; see Table 4).

CAVEAT

By presenting these findings, I in no way suggest that the search for reversibility should be completely abandoned; rather the clinician should understand the slim odds involved in the quest and the potential iatrogenic damage of an overzealous approach. Even when com-

plete reversibility is not reached, a significant improvement in function can occasionally occur after treating the underlying disease. For example, Hedner et al[22] found that the condition of 10 of the 75 patients with dementia assessed in a Swedish geriatrics ward was complicated by a reversible depression. While treatment of the affective disorder did not alleviate the cognitive decline, it did allow discharge of 3 patients.

Neither do the present findings suggest that we ignore the comorbidities that affect so many people with dementia,[66] only that the diagnosis of such accompanying disease not be confused with a quest for dementia reversibility. Clearly all patients who complain of and/or experience any significant sign or symptom should be appropriately assessed and treated, regardless of whether the comorbid condition affects dementia reversibility.

As well, identifying a problem and halting decline, even slightly, with appropriate treatment is always welcome. The patient with cognitive decline should receive a comprehensive assessment when first presenting and at any time thereafter, whenever there is an acute or subacute change in status.

Finally, the present review concerns itself mainly with dementia in the elderly, the patient group where almost all cases of this syndrome are to be found. Clearly, reversibility is more common in younger patients who are less likely to have either AD or a vascular cause and would be more prone to the exotic dementia etiologies, some of which are indeed reversible. Examples include acquired immunodeficiency syndrome dementia complex,[120] hypereosinophilic syndrome,[121] Wilson disease,[122] hypoparathyroidism,[123] adverse effects of valproate therapy in children,[124] the presence of lupus anticoagulant,[125] macroprolactinoma,[126] polycythemia vera,[127] and dural arteriovenous fistula,[128] among others.

However, almost all of these conditions tend to occur in patients aged 20 to 60 years and are accompanied by strong hints in the medical history and/or in findings of physical examination. Reichman and Cummings[129] have offered an interesting algorithmic approach to rare dementia syndromes. However, the occasional existence of such conditions in younger people cannot justify opening Pandora's box for older people.

What are the clinical implications of the present findings? Walstra et al[48] have expressed them well: "First, the very low prevalence of reversible dementia . . . means that the pretest probability of finding actually reversible conditions by routine investigations is very low."[48(p21)] And of critical importance to the frail elderly in whom iatrogenic disease is more likely, they point out that "false positives are more likely."[48(p21)] Especially for the elderly, we must also guard against the ever-present danger of sliding down the clinical cascade[130] and the possibility that testing for uncommon conditions may harm many patients who do not have the disease being sought.[131]

In conclusion, dementia is a common condition in the elderly, especially the very elderly, and the absolute number of cases will continue to grow as the population ages. Every patient with cognitive decline deserves an assessment. However, a new look at an old problem has confirmed and supported the notion that true reversibility is an extremely uncommon characteristic, occurring even more rarely than was thought to be the case even a decade ago. The approach to the patient with dementia must continue to draw from the best that the science and above all the art of medicine has to offer.

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