The Prevalence of White-Matter Lesions on Computed Tomography of the Brain in Demented and Nondemented 85-Year-Olds

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ABSTRACT

The prevalence of white-matter lesions on computed tomography was studied in a representative sample of 85-year-olds living in Gothenburg, Sweden. The study included a psychiatric examination, interview of a close informant, neuropsychological examination, physical examination, comprehensive laboratory tests, electrocardiogram, chest x-ray, computed tomography scan of the head, and cerebrospinal fluid analysis. The diagnoses of dementia and other mental disorders were made according to DSM-III-R criteria. The prevalence of white-matter lesions in demented subjects was 68.9%, and in nondemented, 33.8%. Their prevalence was not increased in any mental disorder other than dementia. All severities of dementia and the subtypes, Alzheimer's disease, vascular dementia, and other types of dementia, had a significantly higher prevalence of white-matter lesions than did nondemented subjects. The risk for dementia, but not its severity, increased with the severity of these lesions. A stepwise logistic regression analysis showed that both white-matter lesions and infarcts on computed tomography contributed independently to dementia.

White-matter changes may be a contributing cause of dementia in the oldest old, or may represent a disease entity of its own. They are important to recognize since they may be potentially preventable, or even treatable. (*J Geriatr Psychiatry Neurol* 1994; 7:169–175).

In a recent report from our group, we found that vascular dementia, related to focal neurologic symptoms and infarcts in the brain, was more common than previously supposed.[1] However, multi-infarct dementia is not the only vascular dementia. The association between white-matter lesions (WMLs) in the brain and dementia has received much attention recently.[2] WMLs may be visualised on computed tomographic (CT) scan of the head appearing as areas of decreased density or attenuation in the periventricular white matter. On histologic examination, the CT findings have been related to narrowing of the lumen of small penetrating arteries and arterioles, and marked demyelination in subcortical white matter.[3,4] The main risk factors for WMLs are vascular diseases, mainly hypertension.[2,3,5] It has been hypothesized that the dementia syndrome associated with WMLs is caused by a disconnection of subcortical-cortical pathways,[2,6,7] giving rise to subcortical[8–10] or frontal lobe[7,10] symptoms.

On CT, and at autopsy, lesions in the white matter have been found in cases with multi-infarct dementia,[5,7,11–14] and Alzheimer's disease,[5,9,11–13,15–19] as well as in nondemented, healthy elderly subjects.[11,16,20,21] WMLs have been associated with increasing age, both in normal elderly and in demented subjects.[3,8,9,11,17,21,22] It has been suggested that lesions in the white matter may also be of importance for the evolution of affective disorders[23,24] and psychosis[25,26] in late life.

The prevalence figures for WMLs on CT are based, so far, on information from studies on healthy volunteers in ages around 70 years of age, on nondemented neurologic patients referred for routine CT evaluation, or on specific patient samples. Furthermore, knowledge about the age-specific prevalence of these changes is still insufficient. Therefore, it is important to study the occurrence of these changes in unselected samples from the general population.

The aim of the present study, which is part of the longitudinal gerontologic and geriatric population studies in Gothenburg,[1,27–29] is to estimate the prevalence of WMLs on CT in a representative urban sample of 85-

Received October 5, 1992. Received revised January 22, 1993. Accepted for publication March 10, 1993.

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year-old subjects and to relate its occurrence to dementia and other mental disorders.

SUBJECTS AND METHODS

Subjects

All 85-year-olds born between July 1, 1901 and June 30, 1902, and registered for census purposes in Gothenburg, Sweden, were invited to take part in a health control (n = 1502). Both people living in the community and at institutions were included. Half of the sample was systematically selected for a psychiatric examination. The basis for selection was the following procedure: all persons in the census register were consecutively (after date of birth) given a number from 1 to 5 or from 11 to 15. Those with numbers 1, 2, 11, 12, or 14 were selected for the psychiatric examination (n = 826). Forty-three subjects died before the examination, leaving an effective sample of 783 subjects. The procedures have been described in more detail previously.[1]

Four hundred ninety-four subjects (63.1% of the effective sample; 143 men and 351 women) were examined by the psychiatrist. Nonparticipants and participants were compared with regard to sex, marital status, 3-year mortality, and registration as a psychiatric outpatient or inpatient in Gothenburg. No significant differences were found with regard to these factors.[1] The mean age at examination was 85.5 years (range 85 years 3 months–86 years 1 month).

All demented (n = 147), and a systematic subsample of 269 nondemented subjects were invited to undergo a CT scan of the head. Subjects who had been examined in a longitudinal study from the age of 70 to 85 years did not have a CT-scan examination if it was not part of a dementia evaluation. These subjects had numbers 1 to 5. Thus, nondemented subjects with numbers 11, 13, and 14 were selected for the CT-scan examinations. One hundred three (70.1%) demented and 136 (50.6%) nondemented accepted. Three CT scans were excluded from the present study for technical reasons. Within the demented and nondemented groups, there were no differences between participants and nonparticipants in the CT examinations with regard to sex, marital status, psychiatric registration, mental disorders, institutionalization, 3-year mortality, history of focal neurologic symptoms, cardiovascular disorders, hypertension, and mean systolic and diastolic blood pressure (Table 1).

Table 1. Comparisons Between Participants and Non-Participants in the CT Examinations

	Nondemented		Demented	
Participant	*Yes*	*No*	*Yes*	*No*
N =	*133*	*136*	*103*	*44*
Sex				
Males	33.8	27.9 NS	26.2	27.3 NS
Females	66.2	72.1 NS	73.8	72.7 NS
Marital status				
Never married	11.3	14.1 NS	16.8	14.0 NS
Married	29.3	19.3 NS	24.8	25.6 NS
Divorced	6.0	13.3 NS	3.0	4.7 NS
Widowed	53.4	53.3 NS	55.5	55.8 NS
Psychiatric registration	9.0	9.6 NS	34.0	31.8 NS
Mood disorders	18.1	23.5 NS	24.3	34.1 NS
Psychotic disorders	6.8	8.8 NS	12.6	18.2 NS
Anxiety disorders	22.6	24.3 NS	23.3	22.7 NS
Psychotropic drugs	38.4	33.8 NS	56.3	56.8 NS
Institutionalization	2.3	1.5 NS	52.4	38.6 NS
Focal neurologic symptoms	10.5	11.8 NS	31.0	20.9 NS
Ischemic heart disease	45.1	42.7 NS	23.5	18.2 NS
Antihypertensive drugs	20.3	22.1 NS	8.7	10.3 NS
Hypertension	21.4	23.5 NS	9.0	10.8 NS
Three-year mortality	23.3	24.3 NS	55.3	54.6 NS
Mean systolic BP	162.6	163.4 NS	150.5	147.6 NS
Mean diastolic BP	80.4	79.9 NS	79.5	77.0 NS

All figures are percentages except blood pressure, which is given in mean values. NS = nonsignificant; BP = blood pressure.

Methods

The study included medical and psychiatric examinations, interview of a close informant, ECG, chest x-ray, an extensive battery of blood tests, CT scan of the head, and a lumbar puncture. Medical records from psychiatric and geriatric institutions, and outpatient departments in Gothenburg were examined by the first author.[1]

All psychiatric examinations were performed by the first author either in the subject's home or at institutions. The interview was semistructured.[1] Psychiatric symptoms and signs were rated in accordance with the Comprehensive Psychopathological Rating Scale (CPRS).[30] The interviews with a close informant were performed by the first author by telephone.[1]

All CT scans were performed without contrast enhancement, and with 10-mm continuous slices. All CT scans were examined by two radiologists (BP and LAA), without knowledge of the diagnoses. One hundred thirty-one CTs were performed on a Philips Tomoscan 310, and 105 CTs, on a General Electric 8800.

Diagnostic Procedures

Dementia and its severity was diagnosed according to the DSM-III-R criteria,[31] using findings from the psychiatric examination and the close informant interview, Alzheimer's disease according to NINCDS-ADRDA criteria,[32] vascular dementia, and other causes according to Erkinjuntti.[33] Information from the physical and psychiatric examinations, close informant interviews, laboratory tests, ECGs, CT scans of the brain, cerebrospinal fluid analyses, and case records was used in the etiologic diagnosis of dementia. The diagnostic procedures have been described in more detail previously.[1]

Other mental disorders were diagnosed according to the DSM-III-R criteria, based on information from the psychiatric examination alone.[34, 35] Depressive disorders included major depressive disorder, dysthymic disorder, and depression NOS. Psychotic disorders included schizophrenic/schizophreniform disorder, delusional disorder, and psychotic disorder NOS. Anxiety disorders included generalized anxiety disorder, phobic disorder, and obsessive-compulsive disorder.[34]

WMLs were defined as periventricular or subcortical areas of decreased attenuation below that expected for normal white matter. The changes were always diffusely distributed within the white matter. Decreased attenuation was subjectively rated as no, mild, moderate, or severe in relation to the attenuation of normal white matter (Figs. 1 to 4). Location was registered as frontal (mainly around the frontal horns

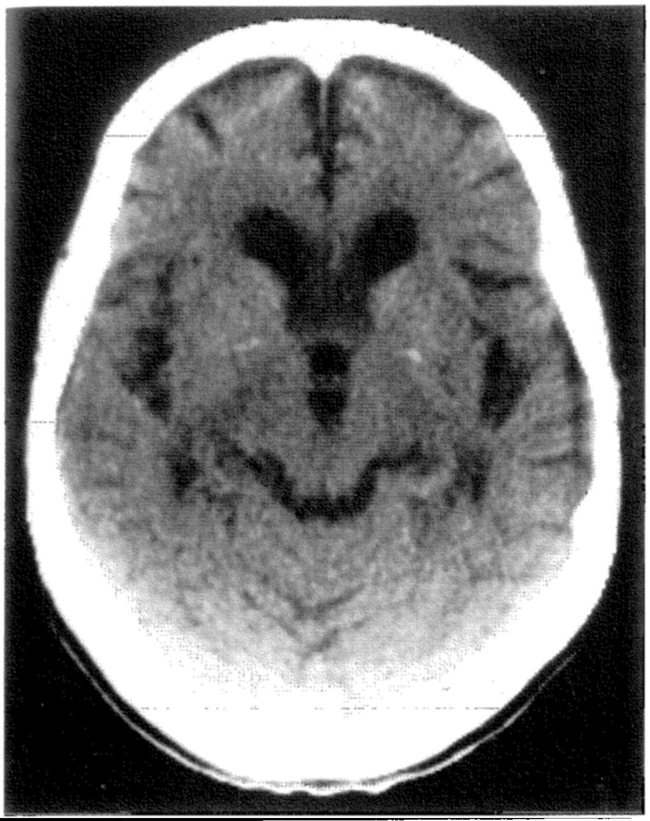

Figure 1. Computed tomography of the brain in an 85-year-old subject without white matter lesions.

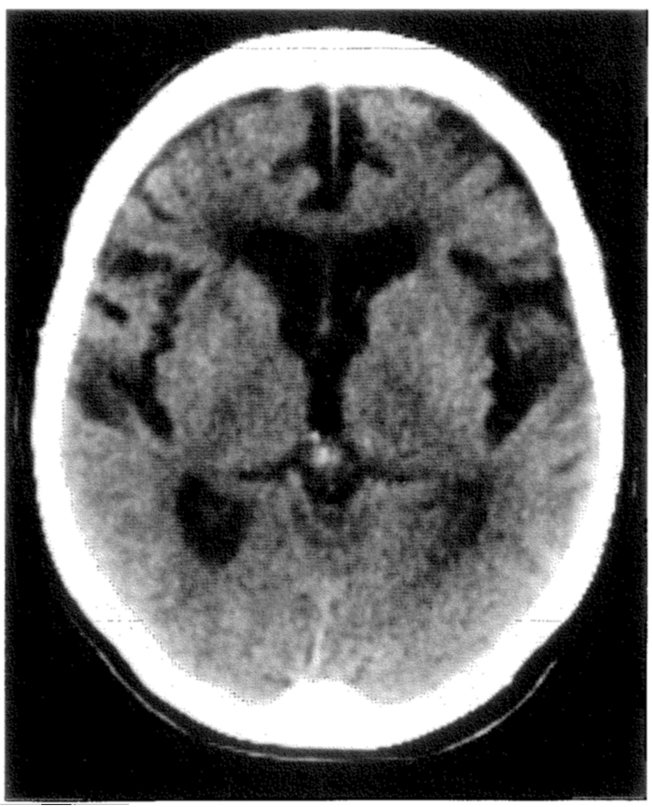

Figure 2. CT of the brain of an 85-year-old subject with mildly decreased attenuation in the white matter around the frontal horns.

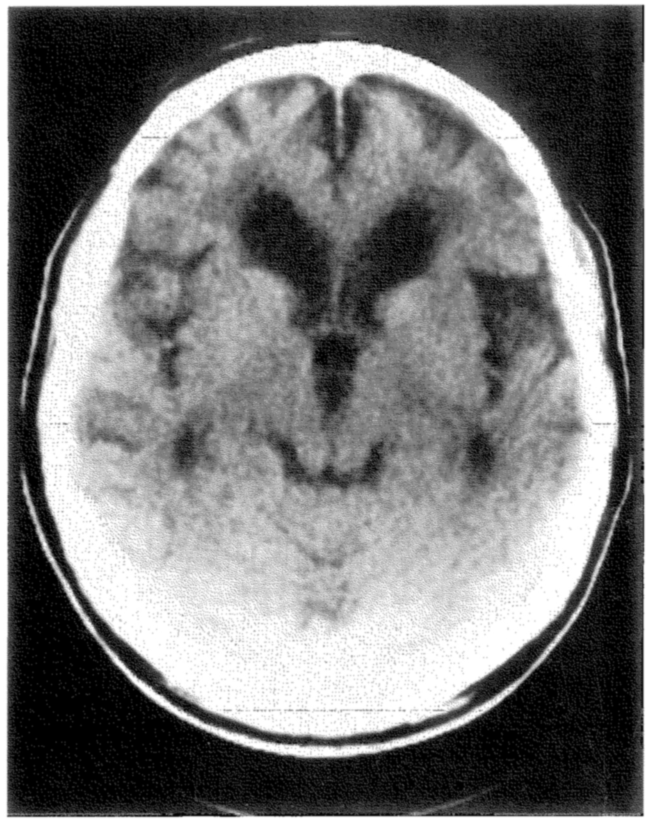

Figure 3. CT of the brain in an 85-year-old subject with moderately decreased attenuation in the white matter around the frontal horns.

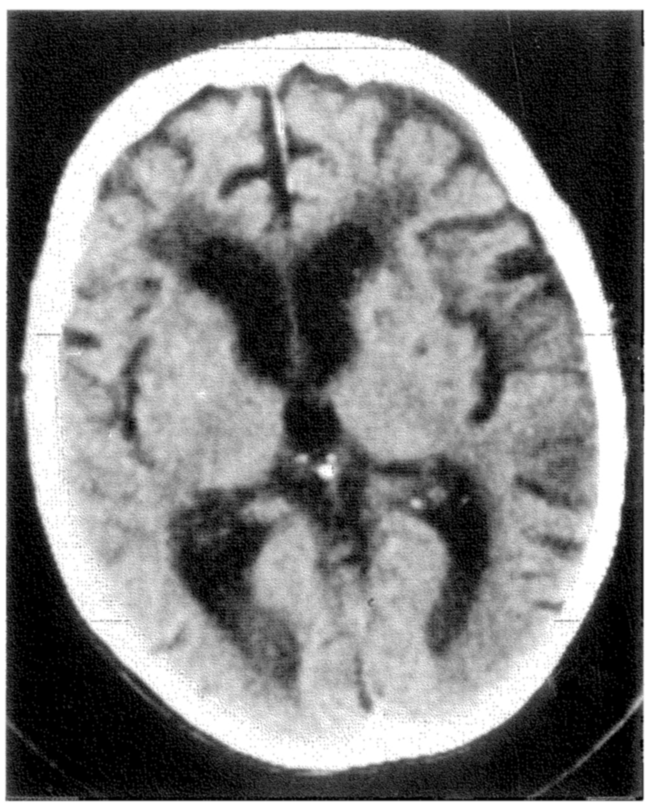

Figure 4. CT of the brain in an 85-year-old subject with severely decreased attenuation in the white matter around the frontal horns.

around the lateral ventricles) or occipital (mainly around the occipital horns around the lateral ventricles).

Inter-observer reliability regarding the occurrence and severity of WMLs was studied in 50 subjects using kappa statistics.[36] Observed agreement was 84.0%, kappa .75 ($P < .001$).

Statistical Methods

Differences in proportions were tested for significance with Fisher's Exact Test. Associations with severity of dementia were tested with Pitman's permutation test.[37] Bayes' theorem[37] was used to calculate the probability for the occurrence of dementia in different grades of decreased attenuation of WMLs. A stepwise logistic regression analysis in a personal computer,[38] using the 5% level of significance, was performed to study the contribution of WMLs and infarcts on CT for the occurrence of dementia. The two-tailed level of significance was used in all analyses.

Informed consent was obtained from all subjects and/or their relatives, and the study was approved by the Ethics Committee for medical research at the University of Gothenburg.

RESULTS

Demented subjects had a significantly higher prevalence of WMLs than did other subjects (Table 2). The prevalence of WMLs was not increased in nondemented subjects with other mental disorders. Demented subjects with concomitant, other mental disorders did not differ from demented subjects without such disorders.

The prevalence of WMLs was 68.9% in demented, and 33.8% in nondemented subjects ($P < .001$) (Table 3). The changes were symmetric in all but five subjects (four demented, and one nondemented) who showed nonsymmetric WMLs. All five subjects had cerebral infarcts. All subjects with WMLs had frontal involvement (n = 116). Thirty-four subjects also had occipital involvement. The latter did not increase the risk for dementia.

The occurrence of WMLs was unaffected by sex, and did not differ significantly between different severities or types of dementia; however, all grades of severity and all types of dementia had significantly higher prevalences of WMLs than did nondemented subjects. If subjects with infarcts on CT were excluded (n = 46), the prevalence of WMLs was 31.0% for nondemented, and 64.9% for demented subjects ($P < .001$).

The risk for dementia in subjects without WMLs was 16%, in subjects with mildly decreased attenuation 35% ($P < .01$), in subjects with moderately decreased attenuation 57% ($P < .001$), and in subjects with severely decreased attenuation 75% ($P < .01$; P = difference against nondemented) (difference between mild and moderate dementia; $P < .05$). There was no relationship between degree of decreased attenuation and severity of dementia.

A stepwise logistic regression analysis was performed to study the contribution of WMLs and infarcts on CT for the occurrence of dementia. The procedure showed that both WMLs ($P < .001$), and infarcts on CT ($P < .05$) contributed independently to the occurrence of dementia.

Table 2. Prevalence of White-Matter Lesions in Relation to Mental Disorders

	WML	Mental Disorder	
	n	n	%
No mental disorder	31	87	35.6
Dementia	71†	103	68.9
Any other mental disorder*	14	46	30.4
Depressive disorders	9	21	42.9
Psychotic disorders	3	9	33.3
Anxiety disorders	5	20	25.0

*A subject might have more than one diagnosis.
†$P < .001$, compared to subjects with no mental disorder.

Table 3. Prevalence of White-Matter Lesions in Relation to Dementia

	WML	Dementia	
	n	n	%
No dementia	45	133	33.8
Dementia	71§	103	68.9
Mild	16*	27	59.3
Moderate	27§	37	73.0
Severe	28§	39	71.8
Cause of dementia			
Alzheimer's disease	23†	36	63.9
Vascular dementia	40§	57	70.2
Other dementias	8*	10	80.0

* $P < .05$; †$P < .01$; and §$P < .001$, compared to nondemented.

DISCUSSION

There were no differences between participants and nonparticipants in the CT-examined sample with regard to a number of factors known to be related to the occurrence of WMLs (Table 1), indicating that the sample was representative of the total group of 85-year-olds. However, the high refusal rate in the nondemented group necessitates the question of representativity to be considered cautiously.

Fifteen studies or case reports* have described the autopsy findings in 55 subjects with WMLs on CT. Of those, 53 had marked demyelination and moderate loss of axons, with gliosis, sparing of subcortical U fibers, and narrowing of the lumen of small penetrating arteries and arterioles in the white matter, caused by hyalinization of the vessel walls in most cases. The findings are similar to those described in Binswanger's disease.[3] Hyperintensities, indicating WMLs, on magnetic resonance imaging (MRI), have been related to less specific autopsy findings,[3,47–49] and not to cognitive decline in the same constant manner as have CT findings.[50,51] The use of CT scan probably resulted in more specific

*References 4,8,10,16,19,21,22,39–46.

findings but a lower prevalence of WMLs than if MRI had been performed.

The prevalence of WMLs in nondemented subjects was 34%. Comparisons with other studies are difficult to do because of methodologic differences.[17] However, the figure is compatible with that of Goto et al,[22] who had 39% in the age group 80 to 89 in a series of consecutive CT examinations (also including demented subjects), but a higher percentage than in normal controls,[11,16,20,21] which may be explained by the lower mean ages of the subjects and the exclusion criteria used in these studies.

The prevalence of WMLs in AD was 64%, which is higher than in studies of AD in younger ages,[9,11–13,16,20,21] but similar to findings in AD of late onset.[9] WMLs on CT are generally more common in late-onset AD than in early-onset,[9,12] suggesting a heterogeneity of AD.[9]

In younger ages, the prevalence of WMLs has been generally higher in vascular dementia than in AD.[12,13,20] We found no such difference, and it is possible that the difference diminishes with increasing age. Our finding that WMLs were present in 70% of vascular dementias is similar to the 46% to 100% found in other studies.[11–13,20]

All cases in the present study had frontal involvement. Most other studies, both on CT[10,21,22] and at autopsy[7,15,18,41] have shown a predominant involvement of frontal white matter.

An association between WMLs and late-onset psychoses[25,26] and affective disorders[23,24] has been suggested. The present study did not demonstrate an increased prevalence of WMLs in any mental disorder other than dementia. Most studies reporting an association between WMLs and late-onset psychosis or mood disorders were performed on MRI. WMLs on MRI may be both quantitatively and qualitatively different from those found on CT, and may reflect alterations in the distribution of intracerebral free water, which may occur in affective disorders,[23] rather than cell loss.

There was an association between the presence and severity of decreased attenuation and the occurrence of dementia, but not with the severity of dementia. The latter is in line with Blennow et al[9] and George et al,[21] but different from Erkinjuntti et al,[12] indicating a complex relationship between dementia and WMLs. It may be that strategic lesions of subcortical pathways[2,6] lead to, or contribute to, dementia, but that other factors determine the severity of dementia.

An overlap with normal aging is also found in other conditions associated with dementia (i.e., senile plaques and neurofibrillary tangles in Alzheimer's encephalopathy[52] and cerebral infarcts in multi-infarct dementia[14]). Although the study showed an increased prevalence of WMLs in demented subjects, this does not establish a causative link. It must still be elucidated whether the presence of WMLs contributes to the dementing process or whether it is only an indirect sign of dementia or aging processes. However, WMLs have been proposed to represent a disease entity of their own,[3] which is generally included among the vascular dementias.[2,3,6] The finding that both infarcts on CT and WMLs contributed independently to dementia gives support to this opinion.

It has been hypothesized that the pathogenesis of WMLs is through hypertension, leading to narrowing of the lumen of small penetrating arteries and arterioles in the brain, through sclerosis and fibrohyaline thickening of the vessel walls. Subsequent hypotension (i.e., by the commonly observed lowering of blood pressure in the elderly, either physiologic or induced by hypotensive drugs, cardiac failure, atrial fibrillation, or disturbances in general health), leads to hypoperfusion and ischemia and loss of myelin in vulnerable areas,[3,4,53] such as the periventricular white matter, which is supplied by long penetrating end-arteries with few collaterals.[3,53] If this hypothesis is correct, WMLs might be amenable to prevention by treatment of hypertension.

Most dementias occur after the age of 80 years. It has been hypothesized that factors other than Alzheimer's encephalopathy may give rise to dementia in these ages.[52] As reported earlier, 47% of all demented subjects in the present study had vascular dementia related to the concept of multi-infarct or mixed dementia.[1] This is the first population-based study on white-matter changes on CT. The finding that white-matter abnormalities was present in 70% of demented subjects might have important implications, since these changes may be more available for prevention and treatment than is Alzheimer's disease at the present time.[2,6]

Acknowledgments

We thank Ms. Liselott Agren for technical assistance. The population study became possible through grants from the Swedish Medical Research Council (Grant nr 90-27X-09131-01A), the Delegation for Social Research within the Ministry of Health and Social Affairs, the Göteborg Medical Services and Social Services Administrations, the Bank of Sweden Tercentenary Foundation, the Stiftelsen Söderström-Königska sjukhemmet, Konung Gustaf V:s och Drottning Victorias Stiftelse, Stiftelsen for Gamla Tjänarinnor, Handlanden Hjalmar Svenssons Forskningsfond, The Swedish Society of Medicine, Stiftelsen Prof Gadelius Minnesfond, The Göteborg Medical Society, Alzheimerfonden, Alma and Anna Yhlén's Foundation.

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