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Predictors of Cognitive Decline and Mortality of Aged People Over a 10-Year Period

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Background. The search for preventable and remediable risk conditions of cognitive decline is ongoing, but results have thus far been inconsistent. According to the hypothesis of our 10-year prospective study, the predictive values of different risk indicators change over time in a general 75+ population.

Methods. A population-based sample of 75-, 80-, and 85-year-old individuals ($n = 650$) underwent comprehensive clinical examinations in 1990 in Helsinki, Finland. Cognitive function was assessed by the Mini-Mental State Examination (MMSE) and/or Clinical Dementia Rating (CDR) at baseline and after 1, 5, and 10 years.

Results. At baseline, a low MMSE score was associated with age, history of stroke, apolipoprotein E allele ε4 (APOE4), and intermittent claudication. After 1 year, cognitive decline was typical of participants suffering from vascular diseases, e.g., heart failure and intermittent claudication. Five-year decline was predicted by the presence of atrial fibrillation (RR [relative risk] 2.8), APOE4 (RR 2.4), elevated C-reactive protein (CRP) (RR 2.3), diabetes mellitus (RR 2.2), and heart failure (RR 1.8). They also tended to increase 5-year all-cause mortality. At 10 years, the decline associated with APOE4 (RR 3.3), slightly elevated serum ionized calcium (RR 3.3), and feelings of loneliness (RR 3.0).

Conclusions. Long follow-up of a general aged population explains several inconsistencies of earlier reports. In 75+ individuals, general ill health is a strong associate of cognitive deficits. The strongest predictors of both cognitive decline and mortality are age, APOE4, manifest vascular diseases, and diabetes. The role of new potential predictors, feelings of loneliness and hypercalcemia, needs clinical testing.

PREVENTION and early recognition of cognitive diseases are of prime importance in aging populations. Both age and genetic factors, such as the presence of apolipoprotein E allele ε4 (APOE4), are powerful risk indicators of Alzheimer's disease (1–8). Cerebrovascular diseases cause cognitive impairment due to overt stroke and other structural brain damage. Also, generalized intermittent claudication has been shown to predispose to dementia including Alzheimer's disease (4,7,9). Consequently, in the search for remediable or preventable risk conditions of cognitive decline, the impact of vascular diseases, especially stroke, and their risk factors is of great interest.

Type 2 diabetes is closely associated with intermittent claudication and has been reported to also predict cognitive decline and dementia (10–15). In contrast, the role of hypertension is controversial (16). While high blood pressure conceivably predisposes to impaired cognition over the long term (15–19), dementia, particularly at an advanced stage, is characterized by low blood pressure (20–22). The same applies to serum cholesterol: While clinical dementia is characterized by relative hypocholesterolemia, hypercholesterolemia may have occurred earlier in middle age (23,24). Although both diabetes and hypertension are intriguing from the pathogenetic perspective of cognitive decline in epidemiological studies, the small performance decrements may not be significant at the individual level (11).

This study was originally designed to test the effects of cardiovascular disease on the "healthy brain" in old age (4,25). Our aim was to identify preventable and treatable risk conditions of cognitive decline after 75 years of age. The secondary aim was to identify how differential mortality affects the relationship between these risk factors and cognitive decline over 10 years of follow-up.

Methods

Study Population and Design

The Helsinki Aging Study is a population-based joint study of general and specialized health care in the City of Helsinki, Finland. A random sample of persons born in 1904, 1909, and 1914 (300 persons/birth cohort) were selected from the census register in 1989. The baseline postal questionnaire included several questions concerning mood and attitudes towards life, for example: "Do you suffer from loneliness?" (seldom or never/sometimes/often or always) and "Do you feel yourself depressed?" (yes or no).

In 1989/1990, 650 participants underwent a comprehensive clinical study including structured examinations of cognition (Table 1).

At entry, participants were examined clinically by a nurse, general practitioner, neurologist, and cardiologist, and the patient records were collected. The clinical examinations have been described in detail earlier (4,25). The participants were reexamined in 1991, 1993 (clinical examination including echocardiography), in 1995 (home visits and Clinical Dementia Rating [CDR]), and in 1999 (home visits including tests for cognition).

Table 1. Study Population and Number of Examinations by Age at Entry, and at 1, 5, and 10 Years

Census Status and Examinations	75 Years	80 Years	85 Years
		At Entry	
Invited	274	266	255
Clinically examined (men)	239 (73)	212 (59)	199 (44)
MMSE	231	200	185
CDR	222	191	184
		1 Year	
Alive	230	198	179
CDR	204	173	160
		5 Years	
Alive	134	84	51
CDR	129	82	47
		10 Years	
Dead	95	136	159
Examined	98	36	18
CDR	98	36	16
MMSE	98	36	16

Note: MMSE = Mini-Mental State Examination; CDR = Clinical Dementia Rating.

Table 2. Percentage Prevalence and Incidence of Cognitive Decline and All-Cause Mortality by Baseline MMSE Score

Variable	MMSE <24 Points	MMSE ≥24 Points	*p* Value
		At Entry	
Age 75 y	19.9	80.1	
80 y	37.0	63.0	
85 y	56.0	44.0	<.001
Gender, Men	29.6	70.4	
Women	38.6	61.4	.041
		At 1 Year	
Mortality	12.6	3.1	<.001
CDR class >0.5	49.5	21.8	<.001
		At 5 Years	
Mortality	57.0	28.3	<.001
CDR class >0.5	50.5	21.7	<.001
		At 10 Years	
Mortality	75.3	49.7	<.001
≥4-point drop in MMSE	44.0	34.1	.341
CDR class >.5	60.0	20.0	<.001

Note: MMSE = Mini-Mental State Examination; CDR = Clinical Dementia Rating.

Assessment of Cognition

The Mini-Mental State Examination (MMSE) (26) and the CDR (27) were used for assessment of cognition. The presence and type of dementia was determined by a neurologist in 1990 (4). Impaired cognition at entry was determined as MMSE <24 points. Cognitive decline was defined either as an increase in CDR class or at least a 4-point decrease in the MMSE score.

Comorbidity (healthy/sick) was not present if the subjective and objective (according to the examining physician) health of the participant was good or moderate, he or she did not have diabetes, or symptoms of vascular diseases, cancer, or other disabling diseases, and he or she had a normal exercise tolerance by history.

Laboratory Examinations

Blood samples for routine laboratory analyses, including plasma lipids, and glycemic data, were drawn after an overnight fast. Calcemic status was determined as ionized serum calcium from the fresh blood sample (28). Apolipoprotein E phenotyping (APOE alleles) was performed from serum samples by immunoelectrophoresis and isoelectric focusing (29). Baseline C-reactive protein (CRP) was measured with a sensitive enzyme immunoassay (sensitivity 0.3 mg/L, Medix Biochemica, Espoo, Finland) from frozen (–20°C) serum samples in 1999 (30).

Statistics

Data were analyzed using the standard Biomedical Data Processing System (31). Differences in proportions were tested with a chi-square test, and continuous measurements with an analysis of variance with covariates. Multiple stepwise logistic analysis was used for testing the risks of mortality and cognitive decline. Because age and gender are important determinants of survival prognosis in old age, these variables were used as covariates in the mortality analyses. The data of cognitive decline were additionally adjusted for baseline MMSE score because mild cognitive deficits appeared to predict further decline. The continuous measurements were summarized as means ± *SEM* (standard error of mean). $P < .05$ was considered statistically significant in the univariate analyses. The alpha-level 0.10 was accepted as significant in the multivariate analyses.

The research protocol was approved by the Ethics Committee of the Helsinki University Central Hospital.

Results

Cross-Sectional Data

The MMSE score decreased with age and was lower in women than men (Table 2). However, the gender differences were insignificant after controlling for age (Table 3). Low scores were typical of individuals with APOE4 and of those without hypertension. Of the apparent vascular diseases, stroke and peripheral intermittent claudication were associated with low MMSE scores. However, no association was found between MMSE scores and history of cardiac diseases or their risk factors.

Prospective Data

Cognition measured using either CDR or MMSE declined consistently with advancing age and lengthening follow-up (Table 2). The most significant associates of cognitive decline appeared to be different according to the baseline age and length of follow-up of patients. Furthermore, the impaired cognition at entry consistently predicted both mortality and further cognitive decline. Therefore, in searching for other significant predictors of cognitive decline, these baseline variables were controlled for age and baseline MMSE.

Table 3. The Baseline MMSE Scores of 629 Participants by Selected Findings

Findings	Number of Participants	MMSE Score	*p* Value
Age (y)			
75	233	25.6 (0.3)	
80	206	23.7 (0.4)	
85	190	21.2 (0.4)	<.001
Gender			
Men	166	23.7 (0.4)	
Women	463	23.6 (0.2)	.834
History of stroke			
No	575	23.9 (0.2)	
Yes	54	19.8 (0.0.7)	<.001
History of myocardial infarction			
No	529	23.7 (0.2)	
Yes	100	23.6 (0.5)	.643
Atrial fibrillation			
No	568	24.1 (0.2)	
Yes	61	24.6 (0.6)	.639
Intermittent claudication			
No	470	24.2 (0.2)	
Yes	159	22.4 (0.4)	.001
Hypertension			
No	400	23.1 (0.3)	
Yes	229	24.2 (0.5)	.014
Diabetes mellitus			
No	528	23.5 (0.2)	
Yes	101	24.3 (0.5)	.157
Plasma insulin			
<11 IU/L	364	23.2 (0.2)	
>11 IU/L	265	24.0 (0.3)	.088
C-reactive protein			
<5 mg/L	549	23.7 (0.3)	
>5 mg/L	80	22.6 (0.6)	.072
Serum cholesterol			
<6.1 mmol/L	396	23.4 (0.3)	
>6.1 mmol/L	233	24.0 (0.3)	.147
APOE4			
No	507	23.9 (0.2)	
Yes	122	22.6 (0.5)	.010
Serum Ca^{++}			
<1.29 mmol/L	562	23.6 (0.2)	
>1.29 mmol/L	67	23.2 (0.6)	.537
Feelings of loneliness			
No	351	24.9 (0.2)	
Yes	180	24.5 (0.3)	.256

Notes: The continuous data are adjusted for age and gender. Mean (*SEM*) in parantheses.

MMSE = Mini-Mental Status Examination; APOE4 = apolipoprotein E allele ε4; Ca = calcium.

One-Year Follow-Up

The CDR class rose in 31% of participants during the first follow-up year. Somatic diseases (comorbidity) were found in the majority (73%) of the participants, and this condition was the most powerful indicator of impaired survival and also a short-term predictor of cognitive decline among the survivors (Table 4).

Table 4. Impacts of Comorbidity on Mortality and Cognitive Decline at Different Time Intervals

	Mortality		Cognitive Decline	
	RR	95% CI	RR	95% CI
1 year	5.71	1.72–18.90	2.09	1.44–3.04
5 years	1.92	1.29–2.86	1.17	0.81–1.69
10 years	2.20	1.51–3.26	1.17	0.76–1.81

Notes: Comorbidity was not present, if the subjective and objective (according to the examining physician) health of the person was good or moderate, he/she did not have diabetes or symptoms of vascular diseases, cancer, or other disabling diseases, and he/she had a normal exercise tolerance by history. The mortality data were adjusted for age and gender and cognitive decline for age and baseline Mini-Mental Status Examination score. The alpha-level 0.10 was accepted as significant in the multivariate analyses.

RR = relative risk; CI = confidence interval.

Closer analysis of components of comorbidity revealed that peripheral intermittent claudication (RR [relative risk] = 2.2 [1.4–3.2]) and heart failure (RR = 1.6 [1.1–2.4]) emerged as significant predictors (data not shown). That was supported by the fact that the symptoms of patients predicting cognitive decline included dyspnea at mild exercise (RR = 2.3 [1.2–4.6]) and claudication (RR = 1.7 [1.1–2.5]).

Five-Year Follow-Up

At 5 years, 30% of surviving participants were reported to suffer from cognitive decline. After controlling for age and MMSE, the presence of atrial fibrillation (RR = 2.9), APOE4 (RR = 2.4), elevated CRP (RR = 2.3), diabetes mellitus (RR = 2.2), and heart failure (RR = 1.8) significantly preceded an increase in CDR class (Table 5). They also tended to increase the all-cause mortality.

Ten-Year Follow-Up

During the 10-year follow-up, 381 (61%) individuals died. Of the 248 survivors, 65% ($n = 160$) were retested for cognition. The baseline data of tested and nontested participants (81% of whom had died) were quite different (Table 6). Most of the conventional risk conditions at baseline, except high serum cholesterol and calcium, predicted the 10-year mortality (Figure 1). For example, only 3.7% and 4.9% of individuals with a history of stroke or diabetes, respectively, at baseline could be reexamined 10 years later.

The mean decrease in the MMSE score over the 10-year period was 3.2 points and was mainly determined by age (Table 7). Of the different variables measured at baseline, both feelings of loneliness and APOE4 were strong predictors of cognitive decline. A 4-point drop in the MMSE score was used as a cut-off point and an indicator for cognitive decline, with serum ionized calcium over 1.29 mmol/L also predicting cognitive deficits. In contrast, history of vascular conditions (hypertension, myocardial infarction, atrial fibrillation, and stroke) did not predict further cognitive impairment, and neither were changes in MMSE score associated with history of type 2 diabetes, fasting blood glucose, plasma insulin, serum lipids, or CRP.

After controlling for age, decline in MMSE score associated with APOE4 (RR = 3.3, 95% CI [confidence

Table 5. Adjusted Risk Ratios of Clinical Conditions for 5-Year Mortality and Cognitive Decline

	Mortality		Cognitive Decline	
	RR	95% CI	RR	95% CI
APOE4	1.41	0.95–2.10	2.43	1.22–8.13
Heart failure	1.76	1.23–2.51	1.83	1.02–3.27
Atrial fibrillation	NS		2.88	1.26–6.06
Intermittent claudication	2.10	1.45–3.04	NS	
Loneliness	NS		1.68, NS	0.93–3.03
Diabetes mellitus	NS		2.18	1.02–4.42
CRP >5 mg/L	1.68	1.02–2.74	2.32	1.01–5.46

Notes: The mortality data were adjusted for age and gender and cognitive decline for age and baseline Mini-Mental Status Examination score.

NS = not significant ($P > .10$); RR = relative risk; CI = confidence interval; CRP = C-reactive protein.

interval] = 1.2–8.9), slightly elevated serum ionized calcium (RR = 3.3, 95% CI = 1.2–9.1), and feelings of loneliness (RR = 3.0, 95% CI = 1.4–6.8).

In stepwise logistic regression analysis, to which age was added as a covariate, the impact of hypercalcemia (RR = 4.03, 95% CI = 1.30–12.53) and loneliness (RR = 3.34, 95% CI = 1.36–8.13) was further increased, whereas the effect of APOE4 was no longer significant ($p = .201$) (Table 8). The results were essentially similar when changes in CDR classes were used as criteria of cognitive impairment (data not shown).

Sensitivity Analyses

Because of the relatively high number of drop-outs in the 10-year follow-up, two assumptions were tested. All drop-outs were allocated either to the group with or without cognitive decline (Table 8). In these analyses, both feelings of loneliness and high serum calcium preserved predictive significance at $p = .10$.

Discussion

Both cross-sectional and follow-up data clearly show that general ill health is associated with cognitive deficits and cognitive decline in a general aged population. They are in accordance with the results of population-based cross-sectional studies showing an association between manifest atherosclerotic diseases and cognitive deficits (3,4,5), but new risk factors for cognitive decline also emerged during long-term follow-up. Of these, the feelings of loneliness and hypercalcemia are potentially treatable. The role of cardiovascular risk conditions remained somewhat ambiguous, and further analyses are needed to assess, for example, the role of blood pressure in this aged study population.

The studies on preventable risk factors of cognitive decline are hampered by several methodological pitfalls. First, case-control studies are often biased because of secondary changes due to dementia and its sequelae. This is exemplified by levels of blood pressure and cholesterol, which tend to diminish with the development of dementia (20–24). Second, the time lag between measurements and end-points can vary widely in the follow-up studies, which may be the most important reason for controversial data on, for instance, the association between cognition and blood pressure. Third, many potential risk factors of cognitive decline, such as stroke, are also associated with mortality, as shown in Table 6. These interrelationships may cause bias, because the excessive mortality of individuals with risk factors of cognitive decline may account for the lack of visibility of these risk factors in prospective studies. In fact, dementia and mild cognitive decline were associated with impaired survival, and APOE4 predicted both dementia and all-cause mortality in

Table 6. Proportions of Participants Not Tested at 10 Years by Baseline Characteristics

Group	Participants Not Available (%)	Difference (%-units)	95% CI (%)
Age (y)			
75	56.2		
80	80.1	−23.9	−32.3, −15.5
85	91.1	−34.8	−42.4, −23.3
Gender			
Men	78.0		
Women	73.0	5.9	−1.5, 13.3
History of stroke			
No	72.5		
Yes	96.3	−23.8	−30.0, −17.6
History of myocardial infarction			
No	73.3		
Yes	81.0	−7.7	−16.2, 0.9
Atrial fibrillation			
No	73.6		
Yes	83.6	−10.0	−20.0, 0.0
Intermittent claudication			
No	69.8		
Yes	88.7	−18.9	−25.3, −12.5
Hypertension			
No	72.0		
Yes	79.0	−7.0	−13.9, −0.2
Diabetes mellitus			
No	60.7		
Yes	95.1	−34.4	−40.0, –28.7
Plasma insulin			
<11 IU/L	71.4		
>11 IU/L	78.9	−7.4	−14.4, −0.1
C-reactive protein			
<5 mg/L	73.0		
>5 mg/L	85.0	−12.0	−20.0, −3.1
Serum cholesterol			
<6.1 mmol/L	79.0		
>6.1 mmol/L	67.0	12.0	4.8, 19.3
APOE4			
Yes	72.4		
No	83.6	−11.2	−18.9, −3.6
Serum Ca^{++}			
<1.29 mmol/L	75.1		
>1.29 mmol/L	70.1	5.0	−6.6, 16.5
Feelings of loneliness			
Yes	48.7		
No	45	3.7	−4.7, 12.2

Note: CI = confidence interval; APOE4 = apolipoprotein E allele ε4; Ca = calcium.

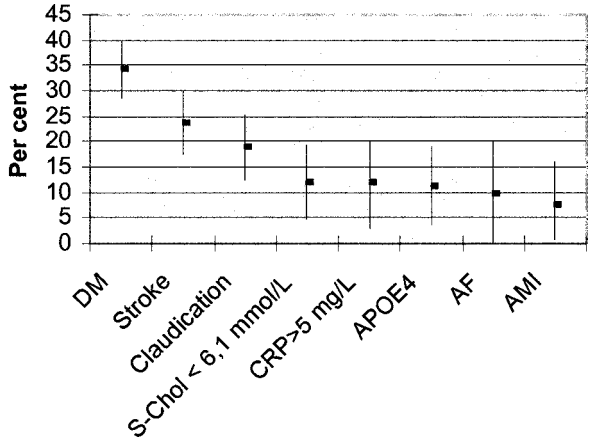

Figure 1. Excess 10-year mortality (%) according to various risk factors at baseline. DM = diabetes mellitus; CRP = C-reactive protein; APOE4 = apolipoprotein E allele ε4; AF = atrial fibrillation; AMI = acute myocardial infarction.

a 5-year follow-up of the present population (4). Furthermore, the majority of stroke patients with cognitive deficits did not survive for 10 years (Table 6). Finally, elevated CRP and low cholesterol levels are related to both dementia and impaired survival (30,32).

The strong attrition in the study population, particularly in the oldest age groups, seen in the high 10-year mortality, decreases the statistical power of the study, and the absence of data on premortal cognitive changes may mask the impact of several important predictors of cognitive decline. On the other hand, our study's strengths are the large size of the original random sample, the comprehensive examinations, and the long follow-up of individuals, already at high risk of cognitive decline at baseline. These provided an excellent opportunity for identifying new risk conditions of cognitive decline, such as loneliness and hypercalcemia. Naturally, both findings may have been detected by chance and by spurious observations due to multiple testing. In any case, evidence exists suggesting that these findings may be of clinical significance.

We have recently reported that, besides cognitive decline, feelings of loneliness also predicted institutionalization among our study population (33). Another recent report has shown that individuals without social network were at risk of developing dementia in a 3-year follow-up period (34). In both studies, loneliness remained an independent risk factor after controlling for depression. The longer follow-up of the present study weakens the possibility that the association between loneliness and dementia is simply due to social withdrawal associated with cognitive decline at baseline. However, few follow-up or intervention studies are available on the prognostic significance of loneliness, and their results have been contentious (35,36). More clinical studies are needed to test whether interventions to relieve loneliness could have an impact on cognitive decline.

The impact of mild hypercalcemia on mortality is minor, and consequently its effects on cognition may only be realized during a sufficiently long follow-up. Calcium dyshomeostasis has been associated with Alzheimer's disease (37), and calcium channel-blocker treatment may protect from dementia (38). Mild hypercalcemia caused by primary hyperparathyroidism (PHP) is common in elderly women (28). Case reports and studies on selected patient groups have actually shown that some neuromuscular, depressive, and other psychiatric symptoms of aged patients with primary hyperparathyroidism may be dramatically improved

Table 7. Changes in MMSE Scores of 160 Surviving Participants by Selected Baseline Findings

Group	Number of Participants	Change in MMSE Score (at 10-year Baseline)	*p* Value
Age (y)			
75	102	−2.8 (0.6)	
80	41	−4.3 (0.9)	
85	17	−6.6 (1.4)	.023
Gender			
Men	35	−2.8 (1.0)	
Women	125	−3.8 (0.5)	.394
History of stroke			
No	158	−3.8 (0.5)	
Yes	2	0.9	ND
History of myocardial infarction			
No	141	−3.6 (0.6)	
Yes	19	−2.2 (1.3)	.31
Atrial fibrillation			
No	150	−3.3 (0.5)	
Yes	10	−2.7 (1.7)	.92
Intermittent claudication			
No	142	−3.2 (0.5)	
Yes	18	−4.1 (1.3)	.51
Hypertension			
No	112	−3.2 (0.5)	
Yes	48	−3.3 (0.8)	.79
Diabetes mellitus			
No	143	−3.2 (0.5)	
Yes	13	−3.2 (1.5)	.95
Plasma insulin			
<11 IU/L	104	−2.3 (0.7)	
>11 IU/L	56	−3.9 (0.7)	.10
C-reactive protein			
<5 mg/L	148	−2.6 (0.6)	
>5 mg/L	12	−3.9 (1.5)	.42
Serum cholesterol			
<6.1 mmol/L	83	−3.2 (0.6)	
>6.1 mmol/L	77	−3.3 (0.6)	.94
APOE4			
Yes	140	−2.8 (0.4)	
No	20	−6.2 (1.1)	.007
Serum Ca^{++}			
<1.29 mmol/L	140	−3.1 (0.5)	
>1.29 mmol/L	20	−4.0 (1.1)	.048
Feelings of loneliness			
No	104	−2.5 (0.5)	
Yes	45	−4.7 (0.8)	.044

Notes: The continuous data are adjusted for age, gender, and baseline MMSE scores. Mean (*SEM*) in parentheses.

ND = not determined; MMSE = Mini-Mental Status Exam; APOE4 = apolipoprotein E allele ε4; Ca = calcium.

Table 8. Sensitivity Analyses of Independent Predictors of 10-Year Cognitive Decline (Drop in MMSE Score $\geq$ 4 Points)

Finding	Risk Ratio (RR)	95% CI
All drop-outs (N = 88) experienced cognitive decline (N = 136)		
APOE4	2.42	0.99–5.88
Serum Ca > 1.29 mmol/L	2.08	0.86–4.98
Feelings of loneliness	1.75	0.92–3.34
None of drop-outs (N = 88) had cognitive decline (N = 200)		
APOE4	NS	$p = .297$
Serum Ca^{++} > 1.29 mmol/L	2.27	0.92–5.65
Feelings of loneliness	2.19	1.05–4.58

Note: NS = not significant ($P > .10$); CI = confidence interval; APOE4 = apolipoprotein E allele ε4; Ca = calcium.

after parathyroidectomy, even in patients with mild hypercalcemia (39). While the effect appears small, the follow-up of aged individuals with mild hypercalcemia is nevertheless warranted to detect those who might later benefit from surgery.

Conclusion

Several somatic diseases are associated with the cognitive decline in old people, and strongest predictors of cognitive decline, such as stroke, are also associated with poor survival in individuals aged 75 or older individuals. Long-term follow-up studies may reveal new, potentially remediable predictors of cognitive decline in this growing age group. The clinical significance of such factors as loneliness and hypercalcemia needs to be tested in future clinical intervention studies.

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