Heterogeneity in Risk Factors for Cognitive Impairment, No Dementia: Population-Based Longitudinal Study From the Kungsholmen Project

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Objectives: *The objectives of this study were to investigate the relation of vascular, neuropsychiatric, social, and frailty-related factors with "Cognitive impairment, no dementia" (CIND) and to verify their effect independently of future progression to Alzheimer disease (AD).* **Methods:** *Seven hundred eighteen subjects aged 75+ years who attended baseline, 3- and 6-year follow-up examinations of the Kungsholmen Project, a Swedish prospective cohort study, were studied. CIND was defined according to the performance on the Mini-Mental State Examination. Potential risk factors were collected at baseline and clustered according to four research hypotheses (frailty, vascular, neuropsychiatric, and social hypothesis), each representing a possible pathophysiological mechanism of CIND independently of subsequent development of AD.* **Results:** *Over a mean 3.4 years of follow up, 82 participants (11.4%) developed CIND. When the population was subsequently followed for a mean of 2.7 years, subjects with CIND had a threefold increased risk to progress to AD. After multiple adjustments, including adjustment for the development of AD at the 6-year follow up, risk factors for CIND were hip fracture, polypharmacy, and psychoses.* **Conclusions:** *The results suggest that not only the AD-type neurodegenerative process, but also neuropsychiatric- and frailty-related factors may induce cognitive impairment in nondemented elderly. These findings may have relevant preventive and therapeutic implications.* (Am J Geriatr Psychiatry 2007; 15:60–69)

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Over the last decade, a great amount of scientific effort has focused on early detection of Alzheimer disease (AD). Individuals who develop a degenerative dementia are likely to undergo a transitional period of cognitive deficits. The concept of cognitive impairment in nondemented subjects has been raised, and different definitions with variable prognosis have been used.[1] Proposed terms such as "cognitive impairment, no dementia" (CIND)[2,3] and "mild cognitive impairment" (MCI)[4] describe cognitive syndromes with high rates of progression to dementia and AD.

A clinic-based study reported an annual progression rate to AD of 12% for MCI subjects in contrast to an annual incidence of dementia of 2% in cognitively intact subjects.[4] Similar data were obtained from population-based studies conducted in subjects with CIND.[3,5] However, as previously reported,[6,7] we also found that the outcome of CIND includes even improvement and that subjects who improved no longer had an increased risk of developing dementia when subsequently followed for three years.[3] These findings suggest that cognitive impairment has heterogenous risk factors.

A comprehensive study of risk factors for cognitive impairment in nondemented subjects may help in better understanding this heterogeneity, but few studies have prospectively addressed this issue on a population level. Older age, low education, being black, depression, apolipoprotein E ε4 allele (ApoE ε4), medicated hypertension, midlife elevated serum cholesterol, high diastolic blood pressure, cortical atrophy, brain infarcts, and white matter hyperintensities have been identified as risk factors for cognitive impairment in dementia-free persons.[8–11]

Within the Kungsholmen Project, we had the opportunity to investigate the longitudinal association among genetic, clinical, neuropsychiatric, and social factors and subsequent development of CIND in an elderly population and to examine whether the associations were independent of future development of AD. Four research hypotheses, each representing possible underlying pathophysiological mechanisms of CIND apart from incipient AD (i.e., conversion within three years), are examined.

Frailty Hypothesis

Because frailty-related factors are associated with low cognitive performance or cognitive impairment,[12,13] we hypothesized that physical dependence, chronic disease, hip fracture, visual and hearing problems, being underweight, and polypharmacy are risk factors for CIND.

Vascular Hypothesis

Vascular diseases and factors (e.g., ApoE ε4) have been reported to be associated with cognitive impairment and cognitive decline in nondemented subjects.[8–11,14] We hypothesized that heart disease, cerebrovascular disease, hypertension, diabetes, obesity, and ApoE ε4 increase the risk of CIND.

Neuropsychiatric Hypothesis

Because depressive symptoms and use of psychotropic drugs have been associated with cognitive decline and cognitive impairment,[8,13,15,16] we hypothesized that psychoses, depressive symptoms, and the use of psychotropic drugs may lead to CIND.

Social Hypothesis

Recent evidence suggests that a socially integrated lifestyle in late life has a beneficial effect on cognition.[17] We hypothesized that infrequent participation in leisure activities and a limited social network increase the risk of developing CIND.

METHODS

Study Population

Data were gathered from the Kungsholmen Project, a longitudinal study of aging and dementia, including all inhabitants of the Kungsholmen district of Stockholm, aged 75+ years on October 1, 1987.[18] Among the 1,700 baseline participants (1987–1989), 225 subjects were prevalent dementia cases and 1,475 were nondemented.[18,19] Of those, 212 subjects had CIND, 31 had low cognitive performance (Mini-Mental State Examination [MMSE] score <20),[20] and nine were excluded because of missing data on ed-

ucation or age >95 years. Thus, the cognitively intact cohort at baseline consisted of 1,223 individuals.[3] Of these, 143 moved or refused to attend the first follow up, which was carried out three years later (1991–1993),[21] 218 persons died before the examination, and 144 developed dementia. The remaining 718 nondemented subjects constituted the study population. The Karolinska Institutet Ethics Committee approved all phases of the Kungsholmen Project, and written informed consent was obtained from all participants at baseline after the procedures had been fully explained.

Definition of Cognitive Impairment

CIND was defined on the basis of the MMSE.[20] Cutoffs for CIND were derived from a previous study[3] and defined as one standard deviation (SD) below the age- and education-specific mean on the test.

Baseline Variables

Demographics, Lifestyles, and Functional Characteristics. Data on age and sex were obtained from the Stockholm municipality office. Education was measured by total years of formal schooling and dichotomized into <8 years and ≥8 years. Leisure activities included social, mental, productive, and fitness activities.[22] Social network comprised elements of marital status, living arrangements, having children, frequency of contact, and satisfaction with such contact.[23] Functional status was measured by Katz' index of activity of daily living (ADL).[24] Sensory function was assessed by physician; hearing impairment was defined as being unable to hear the interviewer's voice (even with a hearing aid), and vision impairment included being blind or almost blind.

Clinical Characteristics and ApoE Genotyping. Information on medical drug use in the 2 weeks before the baseline interview was collected and verified by inspecting drug containers and prescriptions. Drugs were coded according to the Anatomical Therapeutical Classification system (ATC).[25]

Data on medical history were derived from the computerized Stockholm inpatient registry system, which encompassed all discharge diagnoses from hospital admissions in Stockholm since 1969. Diseases from 1969 until baseline were diagnosed according to the International Classification of Diseases, 8th and 9th revisions (ICD-8/ICD-9)[26,27] as follows: chronic obstructive pulmonary disease (ICD-8/ICD-9 codes 490–493), anemia (ICD-8/ICD-9 codes 280–289), malignancy (ICD-8/ICD-9 codes 140–209, 225), arthritis (ICD-8 codes 713–715; ICD-9 codes 715–716), hip fracture (ICD-8/ICD-9 code 820), heart disease (ICD-8 codes 393–398, 410–414, 423–429; ICD-9 codes 393–398, 410–414, 416–417, 423–429), cerebrovascular disease (ICD-8/ICD-9 codes 430–438), hypertension (ICD-8/ICD-9 codes 400–404), diabetes mellitus (ICD-8/ICD-9 code 250), and psychoses (ICD-8/ICD-9 codes 291–298). Clinical diagnoses were grouped as follows:

1. "Vascular disease" included the presence of at least one of heart disease, cerebrovascular disease, diabetes, or hypertension. Diabetes mellitus was defined as the use of blood glucose-lowering medications (ATC code: A10) or a previous diagnosis of diabetes in the inpatient registry. Hypertension was defined as a previous diagnosis in the inpatient registry or according to blood pressure measurements taken at baseline (systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥95 mm Hg).
2. "Chronic disease" included the presence of at least one of the diseases included in the "vascular disease" group or chronic obstructive pulmonary disease, anemia, malignancy, or arthritis.

The presence of current depressive symptoms was assessed by asking the subjects the following questions: "Do you often feel in a low mood?" and "Do you often feel lonely/lonesome?" Both questions belong to the *Center for Epidemiological Studies–Depression Scale*.[28]

Body mass index (BMI) was calculated as the body weight (in kilograms) divided by the square height (in meters). Genomic DNA was extracted from peripheral blood samples, and ApoE genotyping was carried out using a standard polymerase chain reaction.[29]

Diagnosis of Dementia and Alzheimer Disease

For baseline and all follow ups, dementia cases were ascertained by specialists according to *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* criteria[30] with a three-step diagnostic

procedure.[18] Briefly, two examining physicians independently made a preliminary diagnosis, and a third opinion was sought in case of disagreement. The AD diagnosis required gradual onset, progressive deterioration, and lack of any other specific cause of dementia. For deceased subjects, dementia diagnoses were made after reviewing the medical records and death certificates.

Statistical Analysis

Characteristics between subjects with and without CIND at first follow up were compared with two-tailed Pearson chi-squared or independent Student t tests. The progression rates of CIND to AD were calculated as number of events divided by person-years of follow up. A Cox proportional hazard model was constructed to estimate the relative risk (RR) and 95% confidence intervals (95% CIs) of developing AD related to CIND. Different logistic regression models were constructed to estimate odds ratios (ORs) and 95% CIs of CIND related to each risk factor examined in the different hypotheses.

Frailty Hypothesis. Putative risk factors were ADL disability (a score $\geq$1), chronic disease, hip fracture, visual and hearing impairment, being underweight, and number of drugs used. BMI was categorized as underweight (BMI $<$18.5 kg/m^2), normal weight or overweight (BMI 18.5–29.9 kg/m^2), or obese (BMI $\geq$30 kg/m^2).[31] BMI was available for 675 (94%) participants. Number of drugs was categorized as no drug use, 1–4 drugs, and polypharmacy ($\geq$5 drugs).

Vascular Hypothesis. Variables included ApoE ε4, heart disease, cerebrovascular disease, hypertension, diabetes, and obesity. ApoE genotypes were available for 626 (87.2%) persons.

Neuropsychiatric Hypothesis. Factors included psychoses, depressive symptoms, and psychotropic drug use. For depressive symptoms, a combined dichotomized variable was created, in which having none of both symptoms was coded as 0 and having one or two symptoms was coded as 1. Drugs included neuroleptics (ATC code: N05A), anxiolytics (ATC code: N05B), other tranquilizers and hypnotics (ATC code: N05C), and antidepressants (ATC code: N06A).

Social Hypothesis. Variables included social, mental, productive, and fitness activities and social network. Concerning leisure activities, participation in mental and fitness activities was dichotomized into frequent (daily) versus no/infrequent (no/less than daily).[22] Participation in social and productive activities was dichotomized into frequent (daily/weekly) versus no/infrequent (no/less than weekly).[22] The previously used four-grade social network summary index was dichotomized into moderate/extensive versus poor/limited social network.[23]

For each hypothesis, three different logistic regression models were initially implemented: the unadjusted model; the basic-adjusted model with age, sex, education, and time to first follow-up; and the multiple-adjusted model with further control for confounders specific to each hypothesis. In the last model age, sex, education, and time to first follow up represented common confounders for the four research hypotheses. Further factors entered in the *frailty hypothesis* as confounders were depressive symptoms, social network, and ApoE ε4; specific confounders for the *vascular hypothesis* were depressive symptoms, chronic obstructive pulmonary disease, anemia, malignancy, and arthritis; for the *neuropsychiatric hypothesis*, confounders were social network, ApoE ε4, ADL disability, and chronic disease; specific confounders for the *social hypothesis* were depressive symptoms, ADL disability, and chronic disease.

Finally, we further adjusted for the development of AD at the second follow up (three years after CIND occurrence, 1994–1996) to verify whether the effect of various factors was independent of the AD-type neurodegenerative process. As a result of refusal at second follow up (N = 41) and exclusion of other dementias (N = 26), the study sample for these analyses consisted of 651 (90.7%) subjects.

Because the results from the unadjusted and basic-adjusted models overlapped with those from the multiple-adjusted models, we report only the results from the latter.

RESULTS

Of the 718 subjects that were cognitively intact at baseline, 82 (11.4%) developed CIND at first follow up. The mean follow-up time was 3.4 years (SD: 0.5)

without significant difference between subjects with (3.3 ± 0.5 years) and without (3.4 ± 0.5 years) CIND (Student t-test$_{716}$ = −1.192; p = 0.23). At baseline, subjects who developed CIND at first follow up were older and more often reported no/infrequent social and mental activities than cognitively intact subjects (Table 1).

Individuals with CIND had significantly higher prevalence of hip fracture and psychoses and more often used polypharmacy or had depressive symptoms than subjects without CIND (Table 2).

Among the 82 CIND subjects, 20 were diagnosed with AD at the second follow up, with a crude incidence rate of 11.6 per 100 person-years. Of the 636 subjects without CIND, 66 had AD at the second follow up, with a crude incidence rate of 4.0 per 100 person-years. Subjects with CIND had an age, sex, and education adjusted RR of 2.8 (95% CI: 1.7–4.6; Wald $\chi^2_{[1]}$ = 16.7; p <0.0001) to develop AD. The mean follow-up time for the 651 subjects followed at the second follow up was 2.7 years (SD: 0.9) with a significant difference between subjects with (2.4 ± 1.0 years) and without (2.8 ± 0.9 years) CIND at first follow up (Student t-test$_{[649]}$ = −2.993; p = 0.004).

Frailty Hypothesis

Hip fracture and polypharmacy were associated with nearly a threefold increase in the risk of developing CIND, even after controlling for future development of AD (Table 3).

Vascular Hypothesis

None of the vascular risk factors from the hypothesis were significantly associated with the development of CIND, even after adjustment for subsequent development of AD (Table 4).

Neuropsychiatric Hypothesis

Previous psychoses increased the risk of CIND nearly sevenfold. Adjustment for future development of AD did not significantly alter this result (Table 5). Depressive symptoms increased the risk of CIND. However, when subsequent development of AD was entered in the model, this association was no longer significant (Table 5).

Social Hypothesis

No/infrequent social activities almost increased the risk of CIND, but this was no longer significantly present when future AD was entered in the model (Table 5).

DISCUSSION

This study confirms that CIND is characterized by heterogenous risk factors.[8,10] Psychoses, polypharmacy, and hip fracture increased the risk

TABLE 1. Baseline Demographic, Lifestyle, and Functional Characteristics of Subjects With and Without Cognitive Impairment, No Dementia (CIND) at Three-Year Follow Up

Baseline Characteristic	CIND (N = 82)[a]	No CIND (N = 636)[a]	Analyses	p
Age, years (mean, SD)	81.6 (4.5)	80.3 (4.3)	$t_{[716]} = 2.4$	0.020
Female gender	61 (74.4)	471 (74.1)	$\chi^2_{[1]} = 0.004$	0.948
<8 years of education	47 (57.3)	341 (53.6)	$\chi^2_{[1]} = 0.4$	0.527
No/infrequent engagement in				
Social activities	48 (58.5)	289 (45.4)	$\chi^2_{[1]} = 5.0$	0.025
Mental activities	24 (29.3)	117 (18.4)	$\chi^2_{[1]} = 5.4$	0.020
Productive activities	52 (63.4)	406 (63.8)	$\chi^2_{[1]} = 0.006$	0.940
Fitness activities	70 (85.4)	551 (86.6)	$\chi^2_{[1]} = 0.1$	0.752
Poor/limited social network	13 (15.9)	119 (18.7)	$\chi^2_{[1]} = 0.4$	0.530
Activities of daily living disability	19 (23.2)	122 (19.2)	$\chi^2_{[1]} = 0.7$	0.392
Vision problems	32 (39.0)	223 (35.4)	$\chi^2_{[1]} = 0.4$	0.519
Hearing problems	32 (39.5)	253 (40.4)	$\chi^2_{[1]} = 0.02$	0.884

[a]Values are N (%) unless otherwise indicated.

TABLE 2. Baseline Clinical Characteristics and Apolipoprotein E ε4 Allele of Subjects With and Without Cognitive Impairment, No Dementia (CIND) at Three-Year Follow Up

Baseline Characteristic	CIND (N = 82)	No CIND (N = 636)	χ^2 [df]	p
	N (%)	N (%)		
Number of drugs used			$7.3_{[2]}$	0.026
0	9 (11.0)	125 (19.7)		
1–4	46 (56.1)	375 (59.0)		
≥5	27 (32.9)	136 (21.4)		
Chronic obstructive pulmonary disease	1 (1.2)	23 (3.6)	$1.3_{[1]}$	0.256
Anemia	2 (2.4)	19 (3.0)	$0.08_{[1]}$	0.781
Malignancy	7 (8.5)	56 (8.8)	$0.07_{[1]}$	0.936
Arthritis	5 (6.1)	32 (5.0)	$0.2_{[1]}$	0.681
Hip fracture	8 (9.8)	24 (3.8)	$6.1_{[1]}$	0.013
Vascular disease	48 (58.5)	387 (60.8)	$0.2_{[1]}$	0.687
Heart disease	13 (15.9)	83 (13.1)	$0.5_{[1]}$	0.483
Cerebrovascular disease	5 (6.1)	24 (3.8)	$1.0_{[1]}$	0.314
Hypertension	45 (54.9)	323 (50.8)	$0.5_{[1]}$	0.485
Diabetes	4 (4.9)	20 (3.1)	$0.7_{[1]}$	0.411
Chronic disease	52 (63.4)	431 (67.8)	$0.6_{[1]}$	0.429
Psychoses	4 (4.9)	5 (0.8)	$9.8_{[1]}$	0.002
Use of psychotropic drugs	30 (36.6)	216 (34.0)	$0.2_{[1]}$	0.638
Depressive symptoms	33 (40.2)	165 (25.9)	$7.4_{[1]}$	0.006
Body mass index (kg/m^2)			$0.4_{[2]}$	0.818
<18.5	3 (4.1)	29 (4.8)		
18.5–29.9	67 (90.5)	548 (91.2)		
≥30	4 (5.4)	24 (4.0)		
Apolipoprotein E ϵ4 allele (any versus no)	19 (27.9)	138 (24.7)	$0.33_{[1]}$	0.564

Note: The following variables have missing values: body mass index (N = 43) and apolipoprotein E ϵ4 (N = 92).

TABLE 3. Frailty Hypothesis for the Development of Cognitive Impairment, No Dementia (CIND): Odds Ratio (OR) and 95% Confidence Intervals (CIs) for Each of the Frailty-Related Factors

	Multiadjustment[a]			Future Development of Alzheimer Disease Added to the Model[b]		
Risk Factor	OR (95% CI)	Wald χ^2 [df]	p	OR (95% CI)	Wald χ^2 [df]	p
Activities of daily living disability	1.1 (0.6–2.0)	$0.1_{[1]}$	0.727	1.2 (0.6–2.2)	$0.2_{[1]}$	0.649
Chronic disease	0.7 (0.4–1.1)	$2.5_{[1]}$	0.115	0.6 (0.4–1.1)	$2.7_{[1]}$	0.099
Hip fracture	2.8 (1.1–6.9)	$5.0_{[1]}$	0.026	2.9 (1.1–7.8)	$4.3_{[1]}$	0.037
Visual problems	1.0 (0.6–1.6)	$0.3_{[1]}$	0.603	1.0 (0.6–1.7)	$0.05_{[1]}$	0.817
Hearing problems	0.9 (0.5–1.4)	$0.004_{[1]}$	0.950	0.9 (0.6–1.6)	$<0.0001_{[1]}$	0.986
Body mass index (kg/m^2)						
<18.5	0.6 (0.2–2.2)	$0.6_{[1]}$	0.432	1.0 (0.3–3.6)	$<0.0001_{[1]}$	0.996
18.5–29.9	1.0			1.0		
≥30	1.6 (0.5–4.9)	$0.6_{[1]}$	0.439	1.5 (0.4–5.7)	$0.4_{[1]}$	0.523
Number of drugs used						
0	1.0			1.0		
1–4	1.6 (0.8–3.5)	$1.7_{[1]}$	0.197	2.1 (0.9–5.0)	$2.9_{[1]}$	0.088
≥5	2.6 (1.1–6.1)	$5.0_{[1]}$	0.025	3.1 (1.2–8.0)	$5.5_{[1]}$	0.019

[a]OR was adjusted for age, sex, education, time to first follow up, depressive symptoms, social network, apolipoprotein E ε4 allele (any versus no), and other variables listed in the table.

[b]OR was further adjusted for diagnosis of Alzheimer disease made at the second follow-up.

of CIND independently of subsequent development of clinical AD. However, subjects with CIND were at increased risk of developing AD. These findings suggest that CIND is not only a transitional phase between normal aging and AD, but a syndrome with multiple risk factors.

TABLE 4. Vascular Hypothesis for the Development of Cognitive Impairment, No Dementia (CIND): Odds Ratio (OR) and 95% Confidence Intervals (CIs) for Each of the Vascular-Related Factors

	Multiadjustment[a]			Future Development of Alzheimer Disease Added to the Model [b]		
Risk Factor	**OR (95% CI)**	**Wald χ^2 [df]**	**p**	**OR (95% CI)**	**Wald χ^2 [df]**	**p**
Heart disease	1.1 (0.5–2.1)	$0.04_{[1]}$	0.833	1.0 (0.5–2.1)	$0.001_{[1]}$	0.978
Cerebrovascular disease	1.4 (0.5–3.9)	$0.3_{[1]}$	0.559	0.8 (0.2–3.0)	$0.1_{[1]}$	0.748
Hypertension	1.2 (0.8–2.0)	$0.7_{[1]}$	0.417	1.2 (0.7–1.9)	$0.4_{[1]}$	0.547
Diabetes	1.4 (0.4–4.5)	$0.3_{[1]}$	0.564	1.1 (0.3–4.2)	$0.03_{[1]}$	0.862
Body mass index (kg/m^2)						
<18.5	0.8 (0.2–2.7)	$0.2_{[1]}$	0.691	1.1 (0.3–3.8)	$0.1_{[1]}$	0.899
18.5–29.9	1.0			1.0		
≥30	1.4 (0.4–4.3)	$0.3_{[1]}$	0.576	1.4 (0.4–5.2)	$0.3_{[1]}$	0.576
Apolipoprotein E ε4 allele (any versus no)	1.2 (0.7–2.2)	$0.5_{[1]}$	0.470	1.5 (0.8–2.7)	$1.6_{[1]}$	0.212

[a]OR was adjusted for age, sex, education, time to first follow up, depressive symptoms, chronic obstructive pulmonary disease, anemia, malignancy, and arthritis, and other variables listed in the table.
[b]OR was further adjusted for diagnosis of Alzheimer disease made at the second follow-up.

TABLE 5. Neuropsychiatric and Social Hypotheses for the Development of Cognitive Impairment, No Dementia (CIND): Odds Ratio (OR) and 95% Confidence Intervals (CIs) for Each of the Neuropsychiatric- and Social-Related Factors

	Multiadjustment[a]			Future Development of Alzheimer Disease Added to the Model[b]		
Risk Factor	**OR (95% CI)**	**Wald χ^2 [df]**	**p**	**OR (95% CI)**	**Wald χ^2 [df]**	**p**
Neuropsychiatric hypothesis						
Psychoses	6.9 (1.8–27.3)	$7.6_{[1]}$	0.006	5.0 (1.1–23.6)	$4.1_{[1]}$	0.042
Depressive symptoms	1.9 (1.1–3.1)	$6.0_{[1]}$	0.015	1.3 (0.8–2.3)	$1.0_{[1]}$	0.317
Psychotropic drugs use	0.9 (0.6–1.5)	$0.09_{[1]}$	0.770	0.9 (0.5–1.6)	$0.07_{[1]}$	0.798
Social hypothesis						
No/Infrequent social activities	1.6 (1.0–2.6)	$3.6_{[1]}$	0.059	1.4 (0.8–2.3)	$1.2_{[1]}$	0.270
No/Infrequent mental activities	1.5 (0.9–2.6)	$2.1_{[1]}$	0.151	1.5 (0.8–2.7)	$1.6_{[1]}$	0.212
No/Infrequent productive activities	0.8 (0.5–1.4)	$0.5_{[1]}$	0.469	0.7 (0.4–1.1)	$2.3_{[1]}$	0.132
No/Infrequent fitness activities	0.7 (0.4–1.4)	$1.0_{[1]}$	0.322	0.6 (0.3–1.4)	$1.4_{[1]}$	0.235
Poor/limited social network	0.8 (0.4–1.5)	$0.4_{[1]}$	0.506	0.8 (0.4–1.6)	$0.3_{[1]}$	0.562

[a]Neuropsychiatric hypothesis: OR was adjusted for age, sex, education, time to first follow up, social network, apolipoprotein E ε4 allele (any versus no), activities of daily living disability, chronic disease, and other variables listed in the table. Social hypothesis: OR was adjusted for age, sex, education, time to first follow up, depressive symptoms, activities of daily living disability, chronic disease, and other variables listed in the table.
[b]For both hypotheses, OR was further adjusted for diagnosis of Alzheimer disease made at the second follow-up.

Frailty Hypothesis

Among the frailty-related factors, only hip fracture and number of drugs significantly increased the risk of CIND after controlling for future AD. Potential mechanisms underlying these findings could be immobility resulting from hip fracture, which can lead to thromboembolic complications resulting in silent brain ischemic infarcts causing cognitive decline.[32]

Number of drugs used was associated with an increased risk of developing CIND in a dose-response manner, because the risk steadily increased from use of 1–4 drugs to ≥5 drugs. Polypharmacy can be considered an index of comorbidity,[33] and our findings of a threefold increased risk for CIND among persons taking ≥5 drugs strengthens previous reports that comorbidity is associated with cognitive performance in nondemented subjects.[12] Another possible explanation is that polypharmacy per se might cause cognitive deficits.[13]

Vascular Hypothesis

No associations were found between vascular risk factors and the development of CIND in contrast to previous studies.[8–11] This lack of replication might be the result of various reasons. First, the sample size may be not large enough to detect a weak association. Second, previous prospective studies investigating risk factors of MCI were carried out in younger populations.[8–11] The risk effect of vascular diseases on cognitive impairment may be underestimated in the very old as a result of, for example, selective survival (e.g., very old people with vascular comorbidity might have died during the follow-up period, thus being excluded from the analyses). Third, the inpatient registry system may fail to catch some mild cases of vascular disorders (e.g., heart disease and diabetes), which will lead to a dilution of the estimation of the associations.[34,35] Fourth, as a result of lack of neuroimaging in our study, the possible effect of silent brain infarctions was not taken into account.[32]

Neuropsychiatric Hypothesis

Previous psychosis was the major risk factor associated with the development of CIND after controlling for the AD-type neurodegenerative process. Psychotic symptoms and long-term therapy with antipsychotic medication may lead to cognitive impairment and dementia.[13,36] Depressive symptoms were also related to the development of CIND three years later. These data confirm recent findings of an association between depression and MCI.[8] However, our data show that the effect of depressive symptoms on CIND is dependent on the subsequent development of AD, suggesting that the neurodegenerative process underlying the disease may mediate this association. This finding is in line with previous reports in which depressive symptoms occurring more than 25 years before diagnosis were found to be associated with an increased risk of developing AD.[37] Alternatively, depression may be an early sign of AD and cognitive decline.[38]

Social Hypothesis

Subjects who engaged less frequently in social and mental activities tended to have an increased risk of developing CIND. However, this trend for an association disappeared after controlling for future development of AD. These findings agree with evidence demonstrating that a healthy social life can protect against the development of dementia.[17,22,39]

The strengths of our study are the population-based prospective design, the comprehensive analysis of risk factors organized into different etiologic hypotheses, and the adjustment for multiple potential confounders and the ongoing AD-type neurodegenerative process. However, some methodological issues deserve mentioning. First, CIND was determined in persons aged 75+ years at entry. Therefore, our results may not be generalizable to a younger elderly population. Second, information on medical history was mainly taken from the inpatient register system, which would identify more severe cases and miss mild cases. However, our inpatient register covered up to six diseases diagnosed per hospital admission; this may have reduced the possibility of missing information. Third, we could have missed some associations resulting from limited statistical power such as the association with vascular factors. Fourth, CIND was defined according to performance on the MMSE, rather than on clinical judgment, and this could be considered an imprecise measurement of cognitive impairment. However, our previous data showed that this CIND definition significantly predicts dementia over three and six years[3] with a similar proportion of progression rates as other clinical definitions of cognitive impairment.[40] Fifth, because our analyses were exploratory, based on preestablished hypotheses, and run in different models of logistic regression, we did not control for multiple comparisons. Finally, AD was diagnosed according to clinical judgment without autopsy confirmation with uncertainty concerning the rate of diagnostic misclassification.

In conclusion, our study shows that CIND has heterogenous risk factors, in which different pathophysiological mechanisms may be involved. CIND is not only a transitional phase between normal aging and AD, but a syndrome with multiple risk factors in which frailty-related factors and psychiatric disorders seem to play a major role. These findings may have relevant preventive and therapeutic implications.

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References

1. Feldman HH, Jacova C: Mild cognitive impairment. Am J Geriatr Psychiatry 2005; 13:645–655
2. Graham JE, Rockwood K, Beattie BL, et al: Prevalence and severity of cognitive impairment with and without dementia in an elderly population. Lancet 1997; 349:1793–1796
3. Palmer K, Wang HX, Bäckman L, et al: Differential evolution of cognitive impairment in nondemented older persons: results from the Kungsholmen Project. Am J Psychiatry 2002; 159:436–442
4. Petersen RC, Smith GE, Waring SC, et al: Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999; 56:303–308
5. Tuokko H, Frerichs R, Graham J, et al: Five-year follow-up of cognitive impairment with no dementia. Arch Neurol 2003; 60: 577–582
6. Larrieu S, Letenneur L, Orgogozo JM, et al: Incidence and outcome of mild cognitive impairment in a population-based prospective cohort. Neurology 2002; 59:1594–1599
7. Ritchie K, Artero S, Touchon J: Classification criteria for mild cognitive impairment: a population-based validation study. Neurology 2001; 56:37–42
8. Lopez OL, Jagust WJ, Dulberg C, et al: Risk factors for mild cognitive impairment in the Cardiovascular Health Study Cognition Study: part 2. Arch Neurol 2003; 60:1394–1399
9. Tervo S, Kivipelto M, Hanninen T, et al: Incidence and risk factors for mild cognitive impairment: a population-based three-year follow-up study of cognitively healthy elderly subjects. Dement Geriatr Cogn Disord 2004; 17:196–203
10. DeCarli C, Miller BL, Swan GE, et al: Cerebrovascular and brain morphologic correlates of mild cognitive impairment in the National Heart, Lung, and Blood Institute Twin Study. Arch Neurol 2001; 58:643–647
11. Kivipelto M, Helkala EL, Hanninen T, et al: Midlife vascular risk factors and late-life mild cognitive impairment: a population-based study. Neurology 2001; 56:1683–1689
12. Blaum CS, Ofstedal MB, Liang J: Low cognitive performance, comorbid disease, and task-specific disability: findings from a nationally representative survey. J Gerontol A Biol Sci Med Sci 2002; 57:523–531
13. Moore AR, O'Keeffe ST: Drug-induced cognitive impairment in the elderly. Drugs Aging 1999; 15:15–28
14. Knopman D, Boland LL, Mosley T, et al: Atherosclerosis Risk in Communities (ARIC) Study Investigators: cardiovascular risk factors and cognitive decline in middle-aged adults. Neurology 2001; 56: 42–48
15. Sachs-Ericsson N, Joiner T, Plant EA, et al: The influence of depression on cognitive decline in community-dwelling elderly persons. Am J Geriatr Psychiatry 2005; 13:402–408
16. Yaffe K, Blackwell T, Gore R, et al: Depressive symptoms and cognitive decline in nondemented elderly women: a prospective study. Arch Gen Psychiatry 1999; 56:425–430
17. Fratiglioni L, Paillard-Borg S, Winblad B: An active and socially integrated lifestyle in late life might protect against dementia. Lancet Neurol 2004; 3:343–353
18. Fratiglioni L, Viitanen M, Bäckman L, et al: Occurrence of dementia in advanced age: the study design of the Kungsholmen Project. Neuroepidemiology 1992; 11(suppl 1):29–36
19. Fratiglioni L, Grut M, Forsell Y, et al: Prevalence of Alzheimer's disease and other dementias in an elderly urban population: relationship with age, sex, and education. Neurology 1991; 41: 1886–1892
20. Folstein MF, Folstein SE, McHugh PR: 'Mini-Mental State': a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12:189–198
21. Fratiglioni L, Viitanen M, von Strauss E, et al: Very old women at highest risk of dementia and Alzheimer's disease: incidence data from the Kungsholmen Project, Stockholm. Neurology 1997; 48:132–138
22. Wang HX, Karp A, Winblad B, et al: Late-life engagement in social and leisure activities is associated with a decreased risk of dementia: a longitudinal study from the Kungsholmen Project. Am J Epidemiol 2002; 155:1081–1087
23. Fratiglioni L, Wang HX, Ericsson K, et al: Influence of social network on occurrence of dementia: a community-based longitudinal study. Lancet 2000; 355:1315–1319
24. Katz S, Ford AB, Moskowitz RW, et al: The index of ADL: a standardized measure of biological and psychosocial function. JAMA 1963; 185:914–919
25. Guidelines for ATC Classification. Uppsala, Sweden, Nordic Council on Medicines, 1985
26. International Classification of Diseases, Injuries, and Cause of Death, 8th Revision (ICD-8). Geneva, World Health Organization, 1967
27. International Classification of Diseases, Injuries, and Cause of Death, 9th revision (ICD-9). Geneva, World Health Organization, 1987
28. Radloff LS: The CES-D scale: a self-report depression scale for research in the general population. Applied Psychological Measurement 1977; 1:385–401
29. Basun H, Corder EH, Guo Z, et al: Apolipoprotein E polymorphism and stroke in a population sample aged 75 years or more. Stroke 1996; 27:1310–1315
30. Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised. Washington, DC, American Psychiatric Association, 1987
31. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults—The Evidence Report. National Institute of Health Obesity Research, 1998; 6(suppl 2):51–209
32. Vermeer SE, Prins ND, den Heijer T, et al: Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med 2003; 348:1215–1222
33. MacKnight C, Rockwood K: Use of the chronic disease score to measure comorbidity in the Canadian Study of Health and Aging. Int Psychogeriatr 2001; 13(suppl 1):137–142
34. Cowie MR, Fox KF, Wood DA, et al: Hospitalization of patients with heart failure: a population-based study. Eur Heart J 2002; 23:877–885
35. Harris MI: Undiagnosed NIDDM: clinical and public health issues. Diabetes Care 1993; 16:642–652

36. Ostling S, Skoog I: Psychotic symptoms and paranoid ideation in a nondemented population-based sample of the very old. Arch Gen Psychiatry 2002; 59:53–59
37. Green RC, Cupples LA, Kurz A, et al: Depression as a risk factor for Alzheimer disease: the MIRAGE Study. Arch Neurol 2003; 60:753–759
38. Berger AK, Fratiglioni L, Forsell Y, et al: The occurrence of depressive symptoms in the preclinical phase of AD: a population-based study. Neurology 1999; 53:1998–2002
39. Verghese J, Lipton RB, Katz MJ, et al: Leisure activities and the risk of dementia in the elderly. N Engl J Med 2003; 348:2508–2516
40. Panza F, D'Introno A, Colacicco AM, et al: Current epidemiology of mild cognitive impairment and other predementia syndromes. Am J Geriatr Psychiatry 2005; 13:633–644