

1 **Serum coenzyme Q10 and risk of disabling dementia: the Circulatory Risk in**
2 **Communities Study (CIRCS)**

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1 **Abstract**

2 **Objective:** To examine whether coenzyme Q10, a potent antioxidant, is associated with
3 risk of dementia, which has not yet been elucidated.

4 **Approach and Results.** We performed a case-control study nested in a
5 community-based cohort of approximately 6000 Japanese aged 40 to 69 years at
6 baseline (1984-1994). Serum coenzyme Q10 was measured in 65 incident cases of
7 disabling dementia with dementia-related behavioral disturbance or cognitive
8 impairment incident between 1999 and 2004, and in 130 age-, sex- and baseline
9 year-matched controls. Serum coenzyme Q10 was inversely associated with dementia:
10 the multivariate odds ratios (95% confidence intervals) were 0.68 (0.26-1.78), 0.92
11 (0.33-2.56), and 0.23 (0.06-0.86) for individuals with the second, third, and highest
12 quartiles of coenzyme Q10, respectively, as compared with the lowest quartile (*P* for
13 trend =0.05). A similar association was found for the coenzyme Q10/total cholesterol
14 ratio: the respective ORs were 0.67 (0.25-1.78), 0.73 (0.28-1.92), and 0.21 (0.05-0.90)
15 (*P* for trend =0.04).

16 **Conclusions:** Serum coenzyme Q10 levels were inversely associated with risk of
17 disabling dementia. (150 words/150 limit)

18 **Keywords:** coenzyme Q10; antioxidant; dementia; epidemiology; follow-up study

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1 **Introduction**

2 Coenzyme Q10 (CoQ10), or ubiquinone, is a vitamin-like substance synthesized by
3 animal cells. CoQ10 largely exists in the myocardium and plays a role in mitochondrial
4 energy production. It also has an antioxidant function and is widely consumed as a
5 supplement in the United States [1]. In addition to the prescription of CoQ10 as an
6 orphan drug for mitochondrial encephalomyopathy, some evidence exists for a
7 beneficial effect of CoQ10 on several neurologic diseases such as Parkinson disease [2],
8 Huntington disease [3], and Friedreich ataxia [4,5] as well as on improved physical
9 exercise capacity [6] and lowered blood pressure [6,7]. Animal studies have shown a
10 potential benefit of CoQ10 on cognitive function [8-11]. A randomized controlled trial,
11 however, has shown that the supplementation of CoQ10 did not influence cerebrospinal
12 fluid biomarkers in patients with mild-to-moderate Alzheimer disease [12]. Yet,
13 evidence on this issue is still limited, and no prospective study has been performed on
14 the preventive effect of CoQ10 on risk of incident dementia in the general population.

15 In the present study, we hypothesized that because of its antioxidant effect,
16 serum level of CoQ10 is inversely associated with disabling dementia. To test this
17 hypothesis, we conducted a nested case-control study in the Circulatory Risk in
18 Communities Study (CIRCS), a large community-based cohort study of Japanese

1 population.

2

3 **Materials and methods**

4 The CIRCS is an ongoing dynamic community cohort study involving 5 communities in
5 Japan. Details of the CIRCS protocol have been described elsewhere [13]. In this study,
6 we included only 1 community, Kyowa, where disabling dementia surveillance is being
7 carried out, and serum CoQ10 values have been measured. A total of 65 cases of
8 patients who were diagnosed between 1999 and 2004 as having disabling dementia,
9 participated in annual health checkups (baseline) at least 5 years before receiving the
10 dementia diagnosis (ie, between 1984 and 1994), were aged 40 to 69 years at baseline,
11 and provided sera for storage at baseline were identified. The criteria of disabling
12 dementia were the same as those of our previous study [14], which also includes the
13 validation of the criteria and the details of the study protocol. As supplemental analysis,
14 we further classified the dementia cases into cases with and without history of stroke on
15 the basis of the systematic stroke registration system described elsewhere [14]. We
16 excluded individuals aged 70 years or older at baseline, because serum CoQ10 would be
17 likely affected by the baseline age, and residents aged 70 years and over were not
18 invited systematically to the baseline examination. One hundred thirty randomly

1 selected controls whose age (± 3 years), sex, and follow-up time were matched at a ratio
2 of 2:1 with the cases were also identified from the risk set. Venous blood was collected
3 at baseline, and sera were prepared from the blood samples as soon as possible after the
4 blood collection at the checkup sites. The serum samples were collected in 0.3-mL tubes
5 and stored at -80°C until measurement in 2005. Serum CoQ10 was measured using
6 high-performance liquid chromatography (HPLC) at the Public Health Institute of
7 Kochi Prefecture with modification of the reported methods [15]. Briefly, a 10- μL
8 serum sample was pretreated with 380 μL of 2-propanol. After centrifugation at 7000 g
9 for 5 minutes, 10 μL of supernatant was applied to the HPLC system (L-7000 series;
10 Hitachi High-Technologies Corporation, Tokyo, Japan) using a SUPELCOSIL LC-8
11 HPLC Column (Sigma-Aldrich Japan, Tokyo, Japan), an RC-10 reduction column
12 (Shiseido Company, Tokyo, Japan), and an electrochemical detector (SI-2; Shiseido
13 Company). The oxidation potential for the electrochemical detector was 600 mV. The
14 mobile phase consisted of 50 mmol/L sodium perchlorate in methanol/2-propanol
15 (100/10, v/v) with a flow rate of 1 mL/min. Serum total cholesterol was measured at
16 baseline using the Liebermann-Burchard direct method at the Osaka Medical Center for
17 Cancer and Cardiovascular Disease, an international member of the US National
18 Cholesterol Reference Method Laboratory Network (CRMLN) [16].

1 For statistical analyses, we conducted conditional logistic analyses using SAS
2 9.1.3. Service Pack 4 (SAS Institute, Cary, NC, USA) with adjustments for body mass
3 index, smoking status, alcohol consumption, diastolic blood pressure, total cholesterol,
4 diabetes mellitus, and use of medication for hypertension or hypercholesterolemia.
5 Since CoQ10 and total cholesterol were strongly correlated (Spearman $r=0.34$), we also
6 examined the association of the CoQ10/total cholesterol ratio with risk of disabling
7 dementia. All probability values for the statistical tests were 2-tailed, and probability
8 values below 0.05 were considered significant. Informed consent was obtained from
9 community leaders and, verbally, from individual participants according to the
10 guidelines of the Council for International Organizations of Medical Science [17]. The
11 study was approved by the institutional review boards of the Osaka Center for Cancer
12 and Cardiovascular Disease Prevention and of the University of Tsukuba.

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1 **Results**

2 As shown in Table 1, the baseline characteristics did not differ materially between the
3 cases and the non-cases, although diastolic blood pressure levels tended to be higher,
4 and prevalence of cholesterol-lowering medication use, lower for cases than for
5 non-cases.

6 Serum coenzyme Q10 was inversely associated with risk of incident dementia
7 (Table 2). The multivariate odds ratios and 95% confidence intervals were 0.68
8 (0.26-1.78), 0.92 (0.33-2.56), and 0.23 (0.06-0.86), for individuals with the second,
9 third, and highest quartiles of CoQ10, respectively, compared with the lowest quartile
10 (P for trend =0.05). A similar association was observed for the CoQ10/total cholesterol
11 ratio. The respective odds ratios were 0.67 (0.25-1.78), 0.73 (0.28-1.92), and 0.21
12 (0.05-0.90) (P for trend =0.04).

13 As supplemental analysis, we stratified dementia cases into those with history
14 of stroke and those without it. Although the number of cases was limited, the
15 associations were stronger for dementia without stroke for both serum CoQ10 and the
16 CoQ10/total cholesterol ratio. The unadjusted odds ratios and 95% confidence intervals
17 of dementia without stroke were 1.18 (0.37-3.75), 0.50 (0.15-1.70), and 0.46 (0.12-1.74)
18 for individuals with the second, third, and highest quartiles of CoQ10 (p for trend

1 =0.13), and were 0.47 (0.15-1.48), 0.34 (0.11-1.09), and 0.24 (0.06-0.98) for respective
2 quartiles of CoQ10/total cholesterol ratio (p for trend =0.04). The corresponding odds
3 ratios and 95% confidence intervals of dementia with stroke were 0.82 (0.26-2.57), 2.24
4 (0.63-7.96) and 0.35 (0.06-2.05) according to quartiles of CoQ10 (p for trend =0.45),
5 and were 1.68 (0.45-6.29), 2.05 (0.51-8.30) and 0.43 (0.06-2.97) according to quartiles
6 of CoQ10/total cholesterol ratio (p for trend =0.43).

7

1 **Discussion**

2 We found a strong inverse association between serum CoQ10 concentration and risk of
3 disabling dementia in the Japanese population. To date, this is the first prospective study
4 to examine the association between CoQ10 and incident dementia in a general setting.

5 Several animal studies have shown that CoQ10 may have a beneficial effect on
6 dementia progression. In transgenic mice, dietary supplementation with CoQ10 reduced
7 brain oxidative stress and deposition of amyloid plaque or amyloid- β and improved
8 behavioral performance [11]. Rats with damaged hippocampi and cerebral cortices
9 showed an adverse alteration in the markers of oxidative damage, but with
10 supplementation with CoQ10, this alteration was reversed [8]. Thus, CoQ10 has been
11 considered a promising treatment for Alzheimer disease. However, a recent randomized
12 control trial of patients with mild-to-moderate Alzheimer disease did not show that
13 antioxidant treatment, including supplementation with high-dose CoQ10, improved the
14 indices of markers of oxidative stress or of neurodegeneration in the cerebrospinal fluid
15 [12]. Although this finding warrants confirmation by replication studies, when it is
16 taken together with the findings of the present study, we assume that CoQ10 could have
17 a more prominent impact on prevention, rather than on treatment, of dementia.

18 The limitations of this study include (1) the relatively small number of cases,
19 although the associations were strong enough to be detected; (2) the diagnoses of

1 disabling dementia conducted by attending physicians, although such diagnosis by
2 attending physicians was previously validated [14]; and (3) the use of long-stored sera,
3 although a previous study showed that the plasma CoQ10 value was unchanged after
4 being deep-frozen and stored for 3 years [18]. When we excluded the serum samples
5 collected before 1989 (23 cases and 46 matched controls excluded), the results were
6 similar (not shown). Fourth limitation is that we did not classify dementia into
7 Alzheimer type and vascular type. Instead, we have information on dementia with and
8 without history of stroke. The associations seemed stronger for dementia without history
9 of stroke, which needs to be confirmed by further studies. Last, we did not survey the
10 dementia at baseline. However, we constructed the baseline at least 5 years prior to the
11 beginning of dementia survey, so the possibility of reverse causation may be small.

12 The inverse association between serum CoQ10 levels and incident dementia
13 did not directly assure that dietary intake of CoQ10 would prevent dementia.
14 Furthermore, CoQ10 supplements were not generally available in Japan at the era of the
15 baseline period (1984-1994). The impact of dietary or supplementary intake of CoQ10
16 was not tested in the present study, which must be examined by a randomized control
17 trial in the future.

18 In conclusion, the serum level of CoQ10 was inversely associated with

1 disabling dementia in this Japanese general population, which suggests that higher
2 serum CoQ10 levels may have a beneficial effect on prevention of dementia.

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5

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12 full list of CIRCS investigators is presented in reference [13].

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Table 1. Baseline characteristics of dementia cases and non-cases, CIRCS aged 40-69 years.

	Dementia cases	Non-cases	<i>p</i> for difference
Number	65	130	
Age, y	64.5	64.1	0.64
Male gender, %	34	34	1.00
Body mass index, kg/m ²	24.3	24.1	0.77
Current smokers, %	26	22	0.47
Current drinkers, %	28	28	1.00
Systolic blood pressure, mmHg	137	136	0.43
Diastolic blood pressure, mmHg	81	79	0.08
Antihypertensive medication, %	28	33	0.45
Diabetes mellitus, %	14	7	0.12
Serum total cholesterol, mg/dL	205	201	0.53
Cholesterol-lowering medication, %	3	10	0.09
Serum coenzyme Q10*, nmol/L	731	762	0.32
Coenzyme Q10/total cholesterol ratio*, 10 ⁻⁶	138.5	151.4	0.15

*Median values and *p* values for differences tested by the Wilcoxon rank sum test.

Table 2. Age and sex-matched and multivariate adjusted conditional odds ratios and 95% confidence intervals of incident dementia according to quartiles of serum coenzyme Q10 and coenzyme Q10/total cholesterol ratio.

	Men and Women				
	Quartiles of serum coenzyme Q10 (nmol/L)				Trend p
	Q1 228-558	Q2 559-765	Q3 766-1015	Q4 1016-2353	
Median, nmol/L	459	635	850	1253	
Total disabling dementia					
Number of cases	18	20	18	9	
Number of non-cases	32	33	32	33	
Matched OR (95% CI)*	1.0	1.03 (0.47-2.29)	0.94 (0.41-2.14)	0.43 (0.16-1.19)	0.10
Multivariable OR (95% CI)‡	1.0	0.68 (0.26-1.78)	0.92 (0.33-2.56)	0.23 (0.06-0.86)	0.05
	Quartiles of serum coenzyme Q10/total cholesterol ratio (10 ⁻⁶)				Trend p
	Q1 54.1-	Q2 107.6-151.3	Q3 151.4-203.6	Q4 203.7-489.1	
	Median, 10 ⁻⁶	91.2	127.3	173.6	230.7
Total disabling dementia					
Number of cases	21	19	17	8	
Number of non-cases	32	33	33	32	
Matched OR (95% CI)*	1.0	0.80 (0.35-1.81)	0.72 (0.31-1.67)	0.28 (0.09-0.84)	0.02
Multivariable OR (95% CI)‡	1.0	0.67 (0.25-1.78)	0.73 (0.28-1.92)	0.21 (0.05-0.90)	0.04

*Matched with age (± 3 years), sex and baseline-year

‡Multivariable model further includes body mass index, smoking status, alcohol consumption, diastolic blood pressure, diabetes mellitus and medication of hypertension and hypercholesterolemia.

‡Further includes serum total cholesterol.