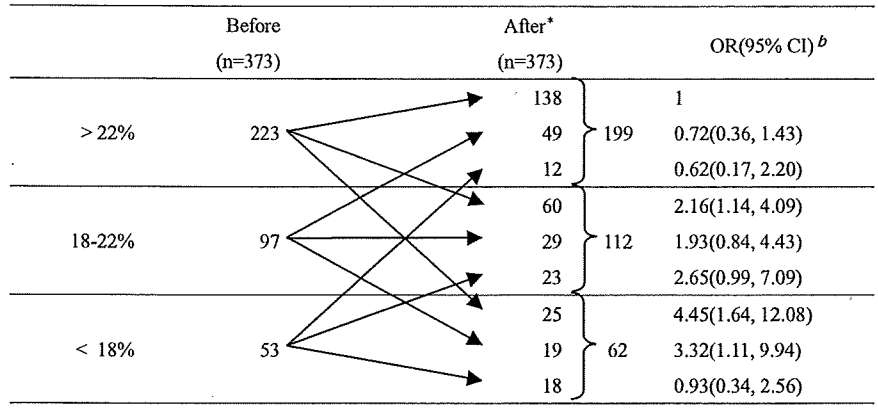


FIG. 1. Number of subjects at before and after dietary intervention according to fat energy ratio (%) (<18%, 18–22%, or >22%) in 373 subjects (305 men and 68 women) [a]. a: Statistical significance is as follows: *, $P < 0.01$ vs. before. b: Odds ratios (OR) adjusted for age, body mass index, physical activity, alcohol use, current smoking status and randomization group, with 95% confidences intervals (CIs) in parentheses.



significant decreasing trend was observed ($P$ for trend = 0.04). Also for LA intake, a significant decreasing trend in OR was observed ($P$ for trend = 0.02), with significantly lower risk in the highest quintile (OR = 0.42, 95% CI = 0.19–0.89). The greatest risk reduction in terms of fatty acid intakes per body weight was observed in LA. For LA intake per body weight, the second (OR = 0.38, 95% CI = 0.18–0.80), the fourth (OR = 0.46, 95% CI = 0.21–0.97), and the fifth (OR = 0.36, 95% CI = 0.17–0.78) quintiles had significantly decreased ORs, all of which were less than half compared with the lowest quintile.

Table 6 shows energy and energy-adjusted nutrient intakes after the intervention in relation to tumor recurrence for women. Significant decreases in OR were found in the highest tertile of SFA (OR = 0.17, 95% CI = 0.04–0.75) and MUFA (OR = 0.12, 95% CI = 0.02–0.60). For linolenic acid (ALA), a significant decreasing trend in OR was observed ($P$ for trend = 0.03). As for LA, ORs for LA intake per body weight in the 2 highest tertiles decreased to less than half, although not significant, compared with the lowest tertile.

At 3 mo after the start of intervention, the mean value and SD of LA intake were 9.5 ± 2.9 g for men and 8.7 ± 2.6 g for women; 25.7% of the subjects overall had fat intakes of less than 7.5 g. Furthermore, no association was found between tumor recurrence risk and eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), or docosahexaenoic acid (DHA) in both men and women. In both sexes, strong correlations were found between LA and SFA, MUFA, PUFA, or ALA ($r = 0.53$, 0.75, 0.96, and 0.91, respectively, $P < 0.01$ for men; $r = 0.62$, 0.73, 0.92, and 0.92, respectively, $P < 0.01$, for women).

## DISCUSSION

This study revealed that the relative risk of recurrence of colorectal tumor after 4 yr was higher in subjects who reduced their fat energy ratio.

TABLE 2
Energy and nutrient intakes of subjects before and after dietary intervention[a]

| | Men ($n$ = 305) | | Women ($n$ = 68) | |
|---|---|---|---|---|
| | Before | After | Before | After |
| Energy (kcal/day) | 2,171 ± 371 | 2,078 ± 344** | 1,770 ± 307 | 1,708 ± 230* |
| Protein (g/day) | 85.9 ± 16.5 | 84.1 ± 15.6 | 72.5 ± 14.8 | 71.3 ± 11.1 |
| Total fat (g/day) | 55.3 ± 15.4 | 51.8 ± 14.3** | 49.6 ± 12.2 | 48.0 ± 10.7 |
| Fat energy ratio (%) | 23.0 ± 5.2 | 22.4 ± 4.9 | 25.3 ± 4.7 | 25.3 ± 4.2 |
| Carbohydrate (g/day) | 278 ± 65 | 267 ± 55** | 250 ± 51 | 239 ± 38** |
| Total fiber (g/day) | 15.0 ± 4.0 | 15.6 ± 4.5** | 16.1 ± 4.5 | 17.1 ± 4.4* |
| Calcium (mg/day) | 636 ± 225 | 603 ± 211** | 699 ± 290 | 681 ± 216 |
| Iron (mg/day) | 11.5 ± 2.8 | 11.0 ± 2.9** | 10.9 ± 3.1 | 10.8 ± 2.5 |
| Carotenoids (μg/day) | 2,809 ± 1,607 | 2,715 ± 1,831 | 3,231 ± 1,727 | 3,075 ± 1,433 |
| Vitamin C (mg/day) | 126 ± 60 | 119 ± 60** | 150 ± 64 | 145 ± 60 |

[a] Values are means ± SD. Statistical significance is as follows: *, $P < 0.05$, **, $P < 0.01$ vs. before.

TABLE 3
Odds ratios (ORs) and 95% confidence intervals (CIs) for tumor recurrence according to quintiles of energy and energy-adjusted nutrient intakes before dietary intervention in men

| | 1 (low; $n = 61$) | 2 ($n = 61$) | 3 ($n = 61$) | 4 ($n = 61$) | 5 (high; $n = 61$) | $P^a$ |
|---|---|---|---|---|---|---|
| Energy intake (kcal/day)[b] | 1,277–1,880 | 1,880–2,062 | 2,062–2,246 | 2,246–2,454 | 2,454–3,855 | |
| No. of cases | 35 | 27 | 33 | 29 | 38 | |
| OR (95% CI)[c] | 1.0 | 0.59 (0.28–1.23) | 0.89 (0.43–1.84) | 0.64 (0.30–1.35) | 1.15 (0.54–2.44) | 0.73 |
| Fat energy ratio (%)[b] | 10.1–18.6 | 18.6–21.6 | 21.6–24.2 | 24.2–27.0 | 27.0–49.5 | |
| No. of cases | 35 | 28 | 36 | 30 | 33 | |
| OR (95% CI)[c] | 1.0 | 0.66 (0.32–1.37) | 1.18 (0.56–2.48) | 0.83 (0.40–1.74) | 0.97 (0.47–2.04) | 0.89 |
| Total fat (g/day)[b] | 6.4–43.5 | 43.5–50.2 | 50.2–56.0 | 56.0–64.4 | 64.4–119.5 | |
| No. of cases | 35 | 26 | 38 | 36 | 27 | |
| OR (95% CI)[c] | 1.0 | 0.58 (0.28–1.20) | 1.41 (0.67–2.97) | 1.32 (0.62–2.81) | 0.63 (0.30–1.32) | 0.93 |
| Saturated fatty acids (g/day)[b] | 0.2–10.6 | 10.6–12.9 | 12.9–15.1 | 15.1–17.6 | 17.6–28.0 | |
| No. of cases | 35 | 33 | 32 | 27 | 35 | |
| OR (95% CI)[c] | 1.0 | 0.90 (0.43–1.87) | 0.91 (0.44–1.89) | 0.61 (0.30–1.28) | 1.17 (0.55–2.46) | 0.86 |
| Monounsaturated fatty acids (g/day)[b] | 0.0–14.1 | 14.1–17.1 | 17.1–19.8 | 19.8–23.1 | 23.1–57.3 | |
| No. of cases | 34 | 34 | 32 | 30 | 32 | |
| OR (95% CI)[c] | 1.0 | 1.05 (0.50–2.17) | 0.97 (0.47–2.00) | 0.81 (0.39–1.68) | 0.96 (0.46–2.01) | 0.41 |
| Polyunsaturated fatty acids (g/day)[b] | 4.3–10.9 | 10.9–12.6 | 12.6–14.3 | 14.3–16.2 | 16.2–30.2 | |
| No. of cases | 33 | 33 | 33 | 30 | 33 | |
| OR (95% CI)[c] | 1.0 | 1.03 (0.50–2.14) | 1.09 (0.53–2.24) | 0.96 (0.46–2.01) | 1.03 (0.50–2.14) | 0.99 |
| Linolenic acids (g/day)[b] | 0.1–1.3 | 1.3–1.5 | 1.5–1.9 | 1.9–2.3 | 2.3–4.0 | |
| No. of cases | 35 | 30 | 38 | 32 | 27 | |
| OR (95% CI)[c] | 1.0 | 0.69 (0.33–1.42) | 1.27 (0.61–2.66) | 0.87 (0.42–1.81) | 0.58 (0.28–1.22) | 0.43 |
| Linoleic acids (g/day)[b] | 3.0–7.8 | 7.8–9.3 | 9.3–10.5 | 10.5–12.0 | 12.0–26.4 | |
| No. of cases | 34 | 36 | 32 | 29 | 31 | |
| OR (95% CI)[c] | 1.0 | 1.17 (0.56–2.47) | 0.95 (0.46–1.97) | 0.75 (0.36–1.57) | 0.87 (0.42–1.82) | 0.24 |
| Linoleic acids per body weight (mg/kg/day)[b] | 61–117 | 117–144 | 144–171 | 171–201 | 201–336 | |
| No. of cases | 37 | 39 | 22 | 34 | 30 | |
| OR (95% CI)[c] | 1.0 | 1.22 (0.58–2.57) | 0.36 (0.17–0.77) | 0.88 (0.42–1.88) | 0.71 (0.33–1.51) | 0.45 |

[a]Test for linear trend.
[b]Values in parentheses are range.
[c]OR adjusted for age, body mass index, physical activity, alcohol use, current smoking status, and randomization group, with 95% CI in parentheses.

Around the period of this study, the Recommended Dietary Allowance (RDA) of fat energy ratio for the Japanese was 20–25% (21). Since we inferred that lower fat intakes would be more beneficial for a high-risk group for colorectal cancer, we took the lowest value of the RDA with 2% margins on both sides and determined our target fat energy ratio of 18–22%. In fact, risk reduction was observed in groups with higher fat energy ratio.

According to the Dietary Reference Intakes of the United States and Canada, based on the results of intervention studies, fat energy ratio of at least 20% is recommended to maintain normal levels of serum lipids such as HDL cholesterol (22). In an intervention study reducing fat energy ratio to 20%, McKeown-Eyssen et al. (10) reported a significant risk reduction (relative risk = 0.6; 95% CI = 0.4–0.9) in the male subjects with the highest fat energy ratio.

Two previous intervention trials have reported no effect of fat restriction on the risk of colorectal tumor recurrence (11,12,23). Compared with those studies, our study was clearly different in that the subjects had a relatively low fat energy ratio at baseline, that is, 23.0% and 25.3% for men and women, respectively. The average fat energy ratio of the Japanese population, even after a rapid increase, is reported to be about 25% (24), which is substantially lower than that of Western people. Besides, our

TABLE 4
Odds ratios (ORs) and 95% confidence intervals (CIs) for tumor recurrence according to tertiles of energy and energy-adjusted nutrient intakes before dietary intervention in women

| | 1 (low; $n = 22$) | 2 ($n = 23$) | 3 (high; ($n = 23$) | $P^a$ |
|---|---|---|---|---|
| Energy intake (kcal/day)[b] | 851–1,646 | 1,646–1,864 | 1,864–2,462 | |
| No. of cases | 10 | 11 | 11 | |
| OR (95% CI)[c] | 1.0 | 0.77 (0.20–2.98) | 0.61 (0.15–2.58) | 0.17 |
| Fat energy ratio (%)[b] | 15.5–23.2 | 23.2–27.7 | 27.7–36.1 | |
| No. of cases | 10 | 11 | 11 | |
| OR (95% CI)[c] | 1.0 | 1.13 (0.31–4.10) | 1.09 (0.27–4.30) | 0.55 |
| Total fat (g/day)[b] | 35.9–52.7 | 52.7–59.1 | 59.1–78.3 | |
| No. of cases | 10 | 11 | 11 | |
| OR (95% CI)[c] | 1.0 | 0.92 (0.25–3.42) | 0.88 (0.22–3.49) | 0.19 |
| Saturated fatty acids (g/day)[b] | 9.1–13.9 | 13.9–17.1 | 17.1–22.8 | |
| No. of cases | 11 | 14 | 7 | |
| OR (95% CI)[c] | 1.0 | 1.87 (0.48–7.29) | 0.24 (0.05–1.14) | 0.63 |
| Monounsaturated fatty acids (g/day)[b] | 11.8–17.6 | 17.6–21.6 | 21.6–28.7 | |
| No. of cases | 10 | 12 | 10 | |
| OR (95% CI)[c] | 1.0 | 1.06 (0.28–3.97) | 0.76 (0.19–2.99) | 0.40 |
| Polyunsaturated fatty acids (g/day)[b] | 8.6–12.8 | 12.8–14.8 | 14.8–23.4 | |
| No. of cases | 9 | 12 | 11 | |
| OR (95% CI)[c] | 1.0 | 2.29 (0.54–9.64) | 1.13 (0.29–4.44) | 0.91 |
| Linolenic acids (g/day)[b] | 1.0–1.5 | 1.5–2.0 | 2.0–3.6 | |
| No. of cases | 9 | 9 | 14 | |
| OR (95% CI)[c] | 1.0 | 1.19 (0.30–4.75) | 2.24 (0.58–8.62) | 0.21 |
| Linoleic acids (g/day)[b] | 5.0–9.3 | 9.3–11.4 | 11.4–19.2 | |
| No. of cases | 9 | 13 | 10 | |
| OR (95% CI)[c] | 1.0 | 2.88 (0.69–11.97) | 0.82 (0.20–3.29) | 0.23 |
| Linoleic acids per body weight (mg/kg/day)[b] | 62–154 | 154–193 | 193–358 | |
| No. of cases | 10 | 13 | 9 | |
| OR (95% CI)[c] | 1.0 | 1.39 (0.38–5.14) | 0.40 (0.09–1.82) | 0.52 |

[a]Test for linear trend.
[b]Values in parentheses are range.
[c]OR adjusted for age, body mass index, physical activity, alcohol use, current smoking status, and randomization group, with 95% CI in parentheses.



subjects had an even slightly lower energy intake and fat energy ratio compared with those of the overall Japanese population according to the National Nutrition Survey in 1999, conducted during this study period (24). This might be explained by our subjects' background; many of them had low levels of physical activity and probably had reduced their fat and meat intake after having been diagnosed with multiple colorectal tumors. Therefore, it is possible that restricting fat in subjects with originally low fat intakes made its harmful effect more evident. It should be noted that this study, as well as other clinical trials with fat restriction discussed here (11,12,22,23), has examined risk of recurrence among the high-risk group for colorectal cancer, namely, the patients who previously underwent multiple tumor resection. Therefore, our results should be interpreted with caution when discussing the initial development of tumors in the general population.

As to the question which specific fatty acid(s) might be involved in it, LA is suspected since we observed the clearest trend of increasing risk as LA intake decreased. With regard to the daily requirement of LA, Collins et al. (25) investigated patients with total parenteral nutrition, who were at risk of LA deficiency, and reported the need for at least 7.5 g/day for adult men. In our study, 25.7% of the subjects did not reach such levels of LA intake. On the other hand, some Japanese researchers have linked excessive LA intake to inflammatory bowel disease, atopy, and asthma, creating such a situation in Japan that food manufacturers have reduced LA content in their oil products (26). Partly because of this situation, it is possible that Japanese people are nowadays easily at risk of LA deficiency. Tuyns et al. (27) reported that LA consistently decreased the risk of colon and rectal cancer in their case-control study in which LA intake among the cases was as low as in our study. In contrast, 3

TABLE 5
Odds ratios (ORs) and 95% confidence intervals (CIs) for tumor recurrence according to quintiles of energy and energy-adjusted nutrient intakes after dietary intervention in men

| | 1 (low; $n = 61$) | 2 ($n = 61$) | 3 ($n = 61$) | 4 ($n = 61$) | 5 (high; $n = 61$) | $P^a$ |
|---|---|---|---|---|---|---|
| Energy intake (kcal/day)[b] | 1,107–1,806 | 1,806–1,972 | 1,972–2,148 | 2,148–2,342 | 2,342–3,240 | |
| No. of cases | 31 | 34 | 31 | 28 | 38 | |
| OR (95% CI)[c] | 1.0 | 1.20 (0.58–2.47) | 0.99 (0.48–2.05) | 0.80 (0.39–1.64) | 1.53 (0.72–3.21) | 0.44 |
| Fat energy ratio (%)[b] | 8.8–18.1 | 18.1–20.9 | 20.9–23.8 | 23.8–26.4 | 26.4–37.9 | |
| No. of cases | 40 | 38 | 35 | 20 | 29 | |
| OR (95% CI)[c] | 1.0 | 0.88 (0.41–1.85) | 0.67 (0.32–1.41) | 0.23 (0.11–0.50) | 0.47 (0.22–0.98) | 0.22 |
| Total fat (g/day)[b] | 12.8–40.6 | 40.6–46.7 | 46.7–53.2 | 53.2–58.9 | 58.9–89.0 | |
| No. of cases | 39 | 39 | 33 | 21 | 30 | |
| OR (95% CI)[c] | 1.0 | 0.97 (0.46–2.04) | 0.62 (0.30–1.30) | 0.27 (0.13–0.59) | 0.50 (0.24–1.05) | 0.08 |
| Saturated fatty acids (g/day)[b] | 3.1–10.2 | 10.2–11.8 | 11.8–13.4 | 13.4–15.9 | 15.9– 29.7 | |
| No. of cases | 40 | 34 | 30 | 34 | 24 | |
| OR (95% CI)[c] | 1.0 | 0.70 (0.33–1.49) | 0.53 (0.25–1.13) | 0.70 (0.33–1.47) | 0.36 (0.17–0.75) | 0.05 |
| Monounsaturated fatty acids (g/day)[b] | 2.0–12.7 | 12.7–15.3 | 15.3–18.0 | 18.0–21.0 | 21.0–35.1 | |
| No. of cases | 38 | 41 | 31 | 25 | 27 | |
| OR (95% CI)[c] | 1.0 | 1.22 (0.57–2.59) | 0.60 (0.29–1.26) | 0.41 (0.19–0.86) | 0.47 (0.22–0.99) | 0.11 |
| Polyunsaturated fatty acids (g/day)[b] | 4.8–9.9 | 9.9–11.7 | 11.7–13.0 | 13.0–15.2 | 15.2–26.3 | |
| No. of cases | 37 | 38 | 33 | 29 | 25 | |
| OR (95% CI)[c] | 1.0 | 1.13 (0.54–2.37) | 0.80 (0.39–1.67) | 0.63 (0.30–1.31) | 0.48 (0.23–1.02) | 0.04 |
| Linolenic acids (g/day)[b] | 0.1–1.1 | 1.1–1.4 | 1.4–1.7 | 1.7–2.1 | 2.1–4.7 | |
| No. of cases | 37 | 28 | 40 | 30 | 27 | |
| OR (95% CI)[c] | 1.0 | 0.58 (0.28–1.21) | 1.31 (0.61–2.80) | 0.68 (0.33–1.42) | 0.55 (0.26–1.16) | 0.46 |
| Linoleic acids (g/day)[b] | 2.0–7.0 | 7.0–8.4 | 8.4–9.6 | 9.6–11.3 | 11.3–20.7 | |
| No. of cases | 40 | 35 | 31 | 30 | 26 | |
| OR (95% CI)[c] | 1.0 | 0.75 (0.35–1.61) | 0.54 (0.26–1.15) | 0.56 (0.26–1.12) | 0.42 (0.19–0.89) | 0.02 |
| Linoleic acids per body weight (mg/kg/day)[b] | 32–107 | 107–128 | 128–151 | 151–181 | 181–337 | |
| No. of cases | 43 | 29 | 32 | 31 | 27 | |
| OR (95% CI)[c] | 1.0 | 0.38 (0.18–0.80) | 0.49 (0.23–1.05) | 0.46 (0.21–0.97) | 0.36 (0.17–0.78) | 0.18 |

[a]Test for linear trend.
[b]Values in parentheses are range.
[c]OR adjusted for age, body mass index, physical activity, alcohol use, current smoking status, and randomization group, with 95% CI in parentheses.

other case-control studies (28–30) and a cohort study (31) did not show such trends regarding LA in particular or n-6PUFA in general. In those studies, LA intake in the subjects was much higher than in our subjects, suggesting no concern regarding LA deficiency.

In addition, there is another factor in relation to the increased risk in the subjects who reduced their fat energy ratio. In one study, a possible role of stress in the development of tumors was suggested (32). If so, radical alteration of diet in our subjects might have given them stress, which promoted to some extent the recurrence of colorectal tumors.

Furthermore, the outcome of dietary instruction was not satisfactory; less than a half of the subjects met our target fat energy ratio of 18–22%. This could be explained as follows. First, the intake of hidden fat contained in meat or fish might not have changed, as subjects had no grasp of it. One study reported that the awareness of subjects regarding fat did not necessarily affect contents of their diet (33). Second, during the time of this study, little information for consumers was available regarding fat content of food items because very few products had fat content labeling (34). Third, our dietary instruction focused on fat restriction, whereas attention to increased intakes of protein and carbohydrate to substitute fat might have been insufficient. As a consequence, our subjects might have reduced the whole intake amount of diet, which affected optimization of fat energy ratio negatively.

TABLE 6
Odds ratios (ORs) and 95% confidence intervals (CIs) for tumor recurrence according to tertiles of energy and energy-adjusted nutrient intakes after dietary intervention in women

| | 1 (low; $n = 22$) | 2 ($n = 23$) | 3 (high; $n = 23$) | $P^a$ |
|---|---|---|---|---|
| Energy intake (kcal/day)[b] | 1,331–1,576 | 1,576–1,788 | 1,788–2,298 | |
| No. of cases | 12 | 10 | 10 | |
| OR (95% CI)[c] | 1.0 | 0.46 (0.11 - 1.86) | 0.33 (0.08 - 1.38) | 0.37 |
| Fat energy ratio (%)[b] | 15.0–22.2 | 22.2–27.3 | 27.3–37.1 | |
| No. of cases | 14 | 11 | 7 | |
| OR (95% CI)[c] | 1.0 | 0.86 (0.22–3.39) | 0.27 (0.07–1.11) | 0.23 |
| Total fat (g/day)[b] | 35.4–49.4 | 49.4–58.6 | 58.6–78.8 | |
| No. of cases | 14 | 11 | 7 | |
| OR (95% CI)[c] | 1.0 | 0.78 (0.20–3.07) | 0.30 (0.08–1.21) | 0.15 |
| Saturated fatty acids (g/day)[b] | 8.1–13.0 | 13.0–15.2 | 15.2–23.1 | |
| No. of cases | 13 | 14 | 5 | |
| OR (95% CI)[c] | 1.0 | 0.96 (0.26–3.60) | 0.17 (0.04–0.75) | 0.32 |
| Monounsaturated fatty acids (g/day)[b] | 10.5–17.0 | 17.0–19.9 | 19.9–29.0 | |
| No. of cases | 15 | 10 | 7 | |
| OR (95% CI)[c] | 1.0 | 0.30 (0.07–1.28) | 0.12 (0.02–0.60) | 0.21 |
| Polyunsaturated fatty acids (g/day)[b] | 6.3–12.1 | 12.1–14.0 | 14.0–20.4 | |
| No. of cases | 11 | 13 | 8 | |
| OR (95% CI)[c] | 1.0 | 1.84 (0.47–7.20) | 0.38 (0.10–1.53) | 0.77 |
| Linolenic acids (g/day)[b] | 0.7–1.6 | 1.6–1.9 | 1.9–2.6 | |
| No. of cases | 12 | 10 | 10 | |
| OR (95% CI)[c] | 1.0 | 0.84 (0.23–3.07) | 0.68 (0.18–2.65) | 0.03 |
| Linoleic acids (g/day)[b] | 5.0–8.9 | 8.9–10.5 | 10.5–16.0 | |
| No. of cases | 12 | 12 | 8 | |
| OR (95% CI)[c] | 1.0 | 1.74 (0.43–7.14) | 0.39 (0.10–1.56) | 0.73 |
| Linoleic acids per body weight (mg/kg/day)[b] | 77–132 | 132–178 | 178–316 | |
| No. of cases | 14 | 10 | 8 | |
| OR (95% CI)[c] | 1.0 | 0.40 (0.10–1.64) | 0.24 (0.06–1.05) | 0.31 |

[a]Test for linear trend.
[b]Values in parentheses are range.
[c]OR adjusted for age, body mass index, physical activity, alcohol use, current smoking status, and randomization group, with 95% CI in parentheses.



There are several weak points in this study. First, our subjects with a history of multiple tumors belonged to the high-risk group, not representing the overall Japanese population.

Second, the primary endpoint was not strictly focused on colorectal cancer but also included adenoma, which was actually observed in most of the cases. For this reason, our results might not be directly applicable to colorectal cancer (carcinoma). However, adenoma is widely accepted as the precursor of cancer based on several findings: histologically, many cases of early carcinoma were detected within adenoma; molecular biologically, adenoma and carcinoma have largely common somatic gene mutations; and epidemiologically, risk factors for the development of adenoma and carcinoma were shown to be common. Thus, we believe that the present study with adenoma as the endpoint is in principle applicable to carcinoma.

Third, this study was subsidiary to another clinical trial aiming to assess the prophylactic effects of wheat bran and/or *Lactobacillus casei*. To find out whether there was any confounding effect of wheat bran or *Lactobacillus casei*, ORs were estimated by applying a logistic regression model to each group separately, showing no difference in the results. Fourth, there was no control group without dietary instruction in this study. Fifth, the sample size of women in this study is rather small. Therefore, our results for women should be interpreted with caution. Sixth, frequency of dietary survey during the 4-yr intervention period was rather low. Since alternative analysis using mean values of 6 days at 3 mo and 4 yr led to the same conclusion, however, the

low frequency of dietary survey is not considered to be a major limitation.

On the other hand, the strong point of this study is the application of a 3-day diet record. Its open-ended question system enabled us to analyze a wide variety of food items reported by the subjects, resulting in high validity of our dietary assessment. Also, the 1-h dietary survey for each subject conducted by a trained dietician ensured that the obtained data were highly accurate. Since this study was performed in one hospital, the test results including colonoscopic evaluation were considered to be consistent. Moreover, the high rate of participation (86.7%) and low dropout rate (4.5%) in this study would have provided less bias in the results.

In conclusion, excessive fat restriction is highly likely to have an undesirable effect in promoting the recurrence of colorectal tumors. According to our results, fat energy ratio of 20% seems to form the turning point in substantially increasing the risk; therefore, we suggest that dietary instruction to reduce fat intake under this level should be defined as excessive fat restriction. Deficiencies in lipids, linoleic acid in particular, and stress caused by dietary alteration might be responsible for this outcome.

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RESEARCH COMMUNICATION

# Risk Factors for Colorectal Cancer in Northeast Thailand: Lifestyle Related

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## Abstract

**Background: The incidence of colorectal cancer is variable around the world. Hiroshima, Japan had the highest incidence in men in 1997 with an age-standardized rate of 86.7 per 100,000 and New Zealand had the highest, at 40.6 per 100,000, in women. The incidence of colorectal cancer in Thailand is rather low and the latest figures for Northeast of Thailand are 7.1 per 100,000 for men and 4.7 for women. The reasons for these differences between countries are possibly due to variation in dietary habits, alcohol drinking or other cofactors. Methods: A case-control study was conducted in Khon Kaen, Northeast Thailand during 2002-2006 to study risk factors for colorectal cancer in a low risk area. Totals of 253 colorectal cancer cases (males 135, females 118) and 253 age- and sex-matched controls were recruited. Information on dietary habits, alcohol drinking, smoking and other information were collected by a structured questionnaire. Blood samples were collected for further study. Both univariate and multivariate analyses were carried out. Results: In the final model of multivariate analysis, the significant risk factors for colorectal cancer were a family history of cancer (OR=1.9 95%CI=1.2-2.9) and meat consumption (OR=1.0 95%CI=1.0007-1.0026). For BMI, subjects with higher BMI unexpectedly had a lower risk of colorectal cancer (OR=0.5 95%CI=0.3-0.8). Conclusion: Our study confirmed risk factors for colorectal cancer i.e. meat consumption and cancer in the family (genetic problem). However, the results for BMI are the reverse of expected, underlining one limitation of hospital-based case-control studies, in which cases are ill and admitted to the hospital at late stage.**

**Key Words:** Colorectal cancer - case-control study - risk factors - Thailand

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## Introduction

The incidence of colorectal cancer is variable around the world. Hiroshima, Japan has the highest incidence in men with the age-standardized rates of 86.7 per 100,000 and New Zealand has a highest incidence in women 40.6 per 100,000 (Parkin et al., 2002). The incidence of colorectal cancer in Thailand is rather low. From population-based cancer registration data in Thailand during 1988-2000 (Vatanasapt et al.,1993; Deerasamee et al.,1999; Sriplung et.at.,2003), colorectal cancer has shown an increasing trend in both males and females in all centers. In 1990, an estimated total of 1,910 new colon cancers occurred in Thailand with a male/female ratio of 1.25 : 1. The annual age-standardized incidence rates were low (5.5 and 3.7 per 100,000 for men and women respectively). For rectal cancer the annual age - standardized incidence rates were also quite low (3.4 and 2.2 per 100,000 for men and women respectively) (Vatanasapt et al., 1993).

In 1999, the estimated annual age-standardized incidence rates of colorectal cancer were 11.8 and 7.8 per 100,000 in males and females respectively (Sriplung et al., 2003). The highest incidence rate of colorectal cancer for both sexes is in Bangkok (age-standardized incidence rate 16.6 for males and 11.0 for females followed by Lampang, Chiang Mai, Songkhla and Khon Kaen which has incidence rates of 7.1 and 4.7 per 100,000 in males and females, respectively. On a world basis, the estimated age-standardised incidence rates by world region in 2002 for South East Asia, with an average incidence similar to that of Thailand, is among the low-risk regions of the world (Ferlay et al., 2004).

The risk of developing colorectal cancer appears to be associated with a diet that is low in fiber and high in calories, protein and fat, especially in red meat. In addition, obesity, sedentary life styles and alcohol consumption have been implicated as potential risk factors (Kinsella, 1993; Potter et al., 1986; Giovannucci et al., 1995). In a study in Bangkok, nitrite-treated meat increased colorectal

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cancer risk; while dietary fibre decreased risk; there was an elevated risk of colorectal cancer in those with a history of bowel polyps (Lohsoonthorn and Danvivat, 1995).

A reduced risk of colorectal cancer has been linked to the use of NSAIDS such as aspirin. (Giovannucci et al., 1995). In Thailand, especially in the Bangkok area, there has been striking change in life style, especially with respect to eating and smoking habits, which may explain the higher incidence rate.

As part of a multi-centre study of 'The epidemiological study of host and environmental factors for stomach and colorectal cancers in Southeast Asian Countries', in this investigation we focused on possible determinants of colorectal cancer in the population of northeast Thailand who came to get treatment at Srinagarind and Khon Kaen Regional Hospital in Khon Kaen Thailand.

## Materials and Methods

*Subjects*

A total of 253 new colorectal cases were recruited from Srinagarind Hospital and Khon Kaen Regional Hospital, Khon Kaen Province, between October 2002 and October 2006. All were from Khon Kaen or neighbouring provinces, histologically confirmed to be colorectal cancers and were interviewed within 3 months of first diagnosis. In the same period, a control was recruited for each case matched by sex, age (± 3 years) and province of residence. Subjects with gastrointestinal disease or other cancers were excluded. All subjects gave informed consent to their participation in the study; subjects who refused, were too old or unable to do the interview were excluded from the study. A 5 ml blood sample was obtained from cases and controls for further study which is not reported in this study. The controls had a variety of diseases, the main ones being diseases of the eye, genito-urinary system and inflammation.

*Interview*

Subjects were interviewed by two trained interviewers, using a structured questionnaire. The questionnaire comprised two sections. The first section included demographic and socio-economic status, smoking history allowing for various periods of different consumption, physical activity, family history. The second section was a food frequency questionnaire structured by meals. The interview referred to habits before the subjects became sick with their present illness (one year earlier). All subjects were reminded of this condition throughout the interview.

*Statistical analysis*

The association between individual variables and colorectal cancer was assessed using conditional logistic regression to account for the matching of cases and controls. A multiple variable model analysis used a backward elimination approach to identify a final set of variables independently associated with colorectal cancer, age, sex and place of resident were included in these analyses, a cut-off level of 0.1 was used to retain variables in the backward elimination approach.

All results are presented as odds ratios (OR) with the associated 95% confidence intervals (95% CI). Those confidence intervals not containing unity were considered statistically significant.

Occupation activity was categorized into 3 levels as heavy labour work, moderate work and light work based on working types. Example, heavy labour workers are persons who are work in farms, gardens, building construction industry etc, moderate workers are persons who mostly work by standing or sitting but move around such as salemen, hair stylists, servants and policeman, and, light workers are persons who mostly sit such as managers and clerks.

For the analysis of cigarette smoking, there were categorized as smokers and nonsmokers. Smokers included those who smoked filtered, unfiltered cigarettes and yamuan (a home-made cheroot). Duration of smoking, and average number of cigarettes per year were computed based on all smoking periods reported and dichotomized on the median of the controls. Average number of cigarette was calculated as annual cigarettes consumption (filtered and unfiltered) plus 1.5 times annual yamuan consumption. The 1.5 correction factor was used to allow for the longer size of yamuan compared with the regular cigarettes. The amount of cigarettes was categorized based on the 50th percentile of the controls and dichotomized into low and high levels.

For the analysis of alcohol drinking, there were two categories for alcohol drinking: drinkers and nondrinkers. Ever drinkers, was defined as who have consumed at least one type of all alcoholic beverages (beer, sato, white alcohol, maekong and other whiskies) and consumed within range of ever day to once a month . Those who did not drink or have consumed all alcoholic beverages with frequently less than one time a month were categorized as nondrinkers.

For the analyses of types of dietary intake within a previous year (vegetable, fruits fish/shellfish: fresh/sea water, meat and fried meat), there were categorized two levels as low and high. Frequencies of each dietary intake, and an amount of intake per year were computed based on each type of dietary intakes reported and dichotomized on the median of the controls.

Body mass index (BMI) was computed as weight (kg) divided by the square of height (m2) which are categorized into two levels (< 25, normal weight and ≥ 25; non-normal; 25 to 29, overweight plus ≥ 30, obese). Exercise was categorized into two levels (exercise and non-exercise) Exercisers were defined as those who played sports at least 3 times a week. Others were considered non-exercisers.

## Results

Table 1 shows the distribution of general characteristics by case and control status. Since this is a matched case-control study, the distributions of age, sex and province of residence were the same in cases and controls. There were 135 males and 118 females, median age is 54. The majority were educated lower than high school. Most of subjects were hard labour workers. The median income per month for both cases and controls are similar (3000

**Table 1. Characteristics of Cases (Colorectal Cancer) and Controls (Patients with Other Diseases)**

| Characteristic | Cases (n = 253) | Controls (n = 253) | $OR_c$ (95 %CI) | $OR_{adj}$ (95 %CI) |
|---|---|---|---|---|
| Male sex, n (%) | 135 (53.4) | 135 (53.4) | | |
| Age group, n (%) | | | | |
| ≤39 | 33 (13.0) | 36 (14.2) | | |
| 40-49 | 60 (23.7) | 51 (20.2) | | |
| 50-59 | 73 (28.9) | 85 (33.6) | | |
| 60-69 | 74 (29.3) | 63 (24.9) | | |
| ≥ 70 | 13 (5.14) | 18 (7.11) | | |
| Median age yr (range) | 54 (4–79) | 55 (6–76) | | |
| Education level, n (%) | | | | |
| ≤ High school | 190 (75.1) | 205 (81.03) | 1.0 | 1.0 |
| > High school | 63 (24.9) | 48 (18.97) | 1.4 (0.9–2.2) | 1.4 (0.9–2.2) |
| Occupation activity, n (%) | | | | |
| Heavy labour work | 176 (70.1) | 177 (70.80) | 1.0 | 1.0 |
| Moderate work (standing) | 43 (17.1) | 43 (17.20) | 1.0 (0.6–1.6) | 1.1 (0.7–1.8) |
| Light work (sitting) | 32 (12.8) | 30 (12.00) | 1.1 (0.6–1.8) | 0.9 (0.5–1.5) |
| Income(Baht) | | | | |
| Median (range) | 3000 (250-80,000) | 3000 (416-45,000) | | |

$OR_c$, Crude Odd Ratio; $OR_{adj}$, Adjusted Odd Ratio; 95% CI, 95% confidence interval; n, number

Baht per month).

Table 2 shows potential risk factors for colorectal cancer from the univariate analysis. Subjects who have relative with cancer have higher risk than those who never have. However, those who have higher BMI have lower risk. Those who have regularly exercise have lower risk for colorectal cancer.

There is a slightly higher risk (non-significant) of colorectal cancer in smokers relative to non-smokers and in smokers of unfiltered cigarettes compared to filtered cigarettes smokers (non significant). There was no evidence of a dose-response effect with respect to duration of smoking or amount smoked.

Most cases (146/253; male, 40 and female, 106) and controls (169/253; male, 57 and female, 112) were non-drinkers. The risk associated with alcohol consumption did not achieve statistical significance.

Table 3 shows univariate analyses of types of dietary intake based on the food frequency questionnaire. Using the low level as referent group, there was association between meat and colorectal cancer. There is no association with other dietary consumption.

Table 4 shows the association between risk factors which found from the multivariate analysis with colorectal cancer. The significant risk factors for colorectal cancer are the history of family with cancer (OR=1.9, 95%CI=1.2-2.9) and meat consumption (OR=1.0, 95%CI=1.0007-1.0026). For BMI, subjects with higher BMI have lower risk for colorectal cancer (OR=0.5, 95%CI=0.3-0.8).

## Discussion

The North East region has been, for many decades, the most impoverished part of Thailand. Until the introduction of various industries in the last 20 years, the

**Table 2. Univariate Analysis of Potential Characteristics Associated with Colorectal Cancer**

| Characteristics | Cases (n = 253) | Controls (n = 253) | $OR_c$ (95% CI) | $OR_{adj}$ (95% CI) |
|---|---|---|---|---|
| Family history of cancer, n (%) | | | | |
| No | 158 (62.7) | 191 (75.8) | 1 | 1 |
| Yes | 94 (37.3) | 61 (24.2) | 1.9* (1.3–2.8) | 1.9* (1.3–2.8) |
| BMI, n (%) | | | | |
| < 25 k/m² | 215 (86.3) | 188 (75.2) | 1 | 1 |
| ≥ 25 k/m² | 34 (13.7) | 62 (24.8) | 0.5* (0.3–0.8) | 0.5* (0.3–0.8) |
| Regularly exercise, n (%) | | | | |
| No | 191 (75.5) | 207 (81.8) | 1 | 1 |
| Yes | 62 (24.5) | 46 (18.2) | 0.7 (0.4–1.1) | 0.7 (0.4–1.1) |
| Ever drink Alcohol, n (%) | | | | |
| No | 146 (57.7) | 169 (66.8) | 1 | 1 |
| Yes | 107 (42.3) | 84 (33.2) | 1.5* (1.02-2.1) | 1.7* (1.1-2.7) |
| Amount of cigarettes per yr, n (%) | | | | |
| None | 133 (54.1) | 140 (56.4) | 1.0 | 1.0 |
| Low (50-4563) | 60 (24.4) | 55 (22.2) | 1.1 (0.7–1.8) | 1.5 (0.5–4.2) |
| High (4,564-25,550) | 53 (21.5) | 53 (21.4) | 1.1 (0.7–1.6) | 1.2 (0.5–2.8) |

$OR_c$, Crude Odd Ratio; $OR_{adj}$, Adjusted Odd Ratio; 95% CI, 95% confidence interval; *P < .05; n, number

**Table 3. Univariate Analysis of Amount of Dietary Intakes Associated with Colorectal Cancer**

| Types (frequency per year) | Cases (n = 253) | Controls (n = 253) | $OR_c$ (95% CI) | $OR_{adj}$ (95% CI) |
|---|---|---|---|---|
| Vegetable/Fruits, n (%) | | | | |
| Low (198-528) | 132 (52.2) | 132 (52.4) | 1.0 | 1.0 |
| High (529-1110) | 121 (47.8) | 120 (47.6) | 1.0 (0.7–1.4) | 1.0 (0.7–1.4) |
| Vegetable Only, n (%) | | | | |
| Low (84-291) | 122 (48.2) | 126 (50.0) | 1.0 | 1.0 |
| High (292-666) | 131 (51.8) | 126 (50.0) | 1.1 (0.8–1.5) | 1.1 (0.7–1.5) |
| Fruit Only, n (%) | | | | |
| Low (42-228) | 137 (54.2) | 136 (53.7) | 1.0 | 1.0 |
| High (229-588) | 116 (45.8) | 117 (46.3) | 1.0 (0.7–1.4) | 1.0 (0.7–1.4) |
| Fish/Shellfish:Fresh/Sea water, n (%) | | | | |
| Low (0-395) | 118 (46.6) | 124 (49.2) | 1.0 | 1.0 |
| High (396-1472) | 135 (53.4) | 128 (50.8) | 1.2 (0.8–1.7) | 1.2 (0.8–1.7) |
| Meat, n (%) | | | | |
| Low (0-238) | 106 (42.0) | 129 (51.0) | 1.0 | 1.0 |
| High (239-2398) | 146 (58.0) | 124 (49.0) | 1.4* (1.0-2.0) | 1.4* (1.0-2.0) |
| Fried Meat, n (%) | | | | |
| Low (0-157) | 119 (48.4) | 128 (51.0) | 1.0 | 1.0 |
| High (158-782) | 127 (51.6) | 123 (49.0) | 1.1 (0.8–1.6) | 1.1 (0.8–1.6) |

OR, odds ratio; $OR_{adj}$, Adjusted Odd Ratio; 95% CI, 95% confidence interval; *P < .05; n, number

population was very largely rural, relying on cultivation of rice, as the staple crop.

Five decades of research into the role of different dietary factors in promoting or preventing cancer have resulted in a broad consensus that fresh fruit and vegetables are protective factors (WCRF, 1997). On this basis, there is little reason to conclude that the low risk of colorectal cancer in North East Thailand is a consequence of a "healthy" diet. Typically, the local diet is based on consumption of sticky rice, which is flavoured with various sauces, often with fermented ingredients and typically rather salty and spiced with liberal use of chilli. Some proteins may be added in the form of meat, fish (generally small fish caught in rivers and ponds). Vegetable consumption is commonly in the form of salads, again flavoured with salty, fermented, spicy sauces. Fruit consumption has not been common, except as incidental snacks (especially banana).

We found slight negative association of vegetable and fruit intake on colorectal cancer which is similar to many studies (Potter et al., 1993; Steinmetz et al., 1996; WCRF 1997).

**Table 4. Final Multivariate Model of Significant Factors Independently Associated with Colorectal Cancer**

| Variables | OR[a] | 95% CI |
|---|---|---|
| Family history of cancer | | |
| No | 1 | |
| Yes | 1.9* | 1.2–2.9 |
| Meat consumption | | |
| Low | 1 | |
| High | 1.0* | 1.0007–1.0026 |
| BMI | | |
| < 25 k/m$^2$ | 1 | |
| ≥ 25 k/m$^2$ | 0.5* | 0.3–0.8 |

[a]Odds ratio based on a backward elimination conditional logistic regression model.*P < .01

There is an association of meat consumption and colorectal cancer in our study which similar to the study in Europe found that those who eat red meat more than 160 g/day has higher risk for colorectal cancer compare to those who consume less than 20 g/day (Norat et al., 2005). Similar finding were found in other studies (Oba et al., 2006; Robertson et al., 2005; Correa et al., 2005; Larsson et al., 2005; Lin et al., 2004).

However these associations were not precise due to the fact that most of our subjects had similar eating habits, thus limiting the ability to assess even the slightest effects of these variables.

An increased risk of colorectal cancer among smokers has been observed in our study but not significant. There are similar finding in numerous studies, both case-control and cohort (Slattery et al., 1990; Tavani et al., 1998; Giovannucci et al., 1994; Akhter et al., 2007). However, the lack of association which is often observed in a hospital-based case-control studies may be due to the high prevalence of smoking related diseases in the control series.

We observed that alcohol drinking was positively associated with colorectal cancer in a univariate analysis but not in multivariate analysis. In a population base prospective cohort study in Singapore (Tsong et al., 2007) found that alcohol consumption is risk for colorectal cancer (hazard ratio = 1.72, 95 % confidence interval = 1.33-2.22). The similar finding also found in other studies (Akhter et al.,2007; Moskal et al., 2007).

We found that people who had relative with cancer have higher risk with colorectal cancer. Similar finding found in many studies (Burt et al., 1985; Slattery et al., 2003; Shah et al., 2007).

BMI, subjects with higher BMI have lower risk for colorectal cancer (OR=0.5, 95%CI=0.3-0.8). This finding seems to be opposite of the finding in a cohort study (Adams et al., 2007) which found that BMI , body mass index (BMI) has been associated with increased risk of

colorectal or colon cancer in men, but the relation is weaker and less consistent for women. However that may due to one of the limitation of hospital-based case-control study that the cases have been ill and admitted to the hospital at late stage, means that cases already weight loss for a long period. Exercise (physical activity) found to be protective for colorectal cancer in univariate analysis but not significant similar to the study of Friedenreich et al.(2006).

In conclusion, our study confirmed the risk factors for colorectal cancer i.e. meat consumption, cancer in the family (genetic problem). But the BMI seems to be reverse finding that might due to one of the limitation of hospital-based case-control study that the cases have been ill and admitted to the hospital at late stage. We do not find the association with vegetable/fruit intake on colorectal cancer risk. We do not find the association with food preparations on colorectal cancer risk. We observed a slightly higher risk for smokers and alcohol drinkers compared to the nonsmokers and nondrinkers. These associations were not precise due to the fact that most of our subjects had similar eating habits, thus limiting the ability to assess even the slightest effects of these variables.

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# Loss of Fractal Heart Rate Dynamics in Depressive Hemodialysis Patients

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**Objective:** To assess the relationship between depression, reduced heart rate (HR) variability, and altered HR dynamics among patients with end-stage renal disease who are receiving hemodialysis (HD) therapy. **Methods:** We analyzed the 24-hour electrocardiograms of 119 outpatients receiving chronic HD. HR variability was quantified with the standard deviation of normal-to-normal R-R intervals, the triangular index, and the powers of the high- (HF), low- (LF), very-low (VLF), and ultra-low frequency (ULF) components. Nonlinear HR dynamics was assessed with the short-term ($\alpha_1$) and long-term ($\alpha_2$) scaling exponents of the detrended fluctuation analysis and approximate entropy. The depression level was assessed using the Beck Depression Inventory, Second Edition (BDI-II). HR variability and dynamics measurements were compared by gender, diabetes, and depression with adjustment for age and serum albumin concentration. **Results:** Most indices of HR variability and dynamics were negatively correlated with age, serum albumin concentration, depression score, and were lower in women and patients with diabetes. The $\alpha_2$ was inversely associated with these variables. Depressed men had significantly lower HF, LF, VLF, and marginally lower ULF than nondepressed persons after adjustment for diabetes and other covariates; no difference in depression was observed in women. The $\alpha_2$ showed marginally significant difference in depression independent from gender and diabetes. **Conclusions:** Among the patients who received HD, depression is associated with reduced HR variability and loss of fractal HR dynamics. However, the influence of depression on HR variability may vary by gender and physiological backgrounds. Further prospective studies are necessary to confirm their association with poor prognosis. **Key words:** depression, fractal, heart rate variability, hemodialysis, nonlinear.

**CHD** coronary heart disease; **HR** heart rate; **DFA** detrended fluctuation analysis; **ApEn** approximate entropy; **HD** hemodialysis; **ESRD** end-stage renal disease; **NKC** Nagoya Kidney Center; **AMI** acute myocardial infarction; **ECG** electrocardiography; **PCR** protein catabolic rate; **SDNN** standard deviation of normal-to-normal R-R intervals; **HF** high-frequency band; **LF** low-frequency band; **VLF** very-low-frequency band; **ULF** ultra-low-frequency band; **SD** standard deviation; **mNN** mean normal-to-normal R-R intervals; **BDI** Beck Depression Inventory; **DSM** Diagnostic and Statistical Manual of Mental Disorders; **ANCOVA** analysis of covariance; **GLM** general linear model.

## INTRODUCTION

Depression is a risk factor for the etiology and prognosis of coronary heart disease (CHD) (1,2). Although the underlying mechanisms are not yet fully understood, an imbalance of the autonomic nervous system in depressed patients is one possible explanation (3,4). Heart rate (HR) variability analysis is commonly used as an index of cardiac autonomic function (5), and reduced HR variability is known to predict mortality in patients with CHD (6,7). In addition, a significant association between depression and low HR variability among this population has been consistently reported (8–12).

Conventionally, HR variability is evaluated using time-domain and frequency-domain analyses. In healthy individuals, normal HR fluctuations are suggested to be neither strictly regular nor completely random, but have a fractal-like structure characterized by self-similarity and scale invariance, that is, the presence of similar dynamics operating over multiple time scales (13). Methods based on a nonlinear system theory have been developed to evaluate qualitative fluctuation characteristics, whereas the traditional time-domain and frequency-domain HR variability analyses assess fluctuation quantity. Detrended fluctuation analysis (DFA) describes fluctuation fractal correlation properties, whereas approximate entropy (ApEn) is an index of overall complexity and time-series predictability. Importantly, nonlinear analyses of HR dynamics have been suggested to provide more powerful prognoses and to detect valuable physiologic and pathophysiologic information that is not achieved by conventional HR variability analysis (5,14,15). Loss of fractal HR dynamics was associated with an increased risk of mortality in patients with (16–19) and without (20) structural heart disease, and in post stroke patients (21).

We previously reported a J-curve relationship between cardiac mortality and the long-term scaling exponent ($\alpha_2$) derived from DFA in hemodialysis (HD) patients with CHD (22). Both increases and decreases of $\alpha_2$, indicating loss of fractal HR dynamics, were significantly associated with the risk of cardiac death; these associations were independent of those of clinical variables. Patients with end-stage renal disease (ESRD) who receive HD are thought to be vulnerable to emotional disturbances because they suffer from chronic stress relating to dietary constraints, time restrictions, functional limitations, various illnesses, and adverse effects of medications (23). Moreover, depression has been suggested as a possible independent risk factor of increased mortality in this population (24). These observations indicate that altered

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HR dynamics might be related to the link between depression and increased mortality among ESRD patients who receive HD. However, to date, only a few studies involving limited numbers of subjects have reported an association between HR dynamics and depression in patients with major depression and in the elderly with cardiac diseases (24–26).

The present study examined whether altered HR dynamics, as assessed by fractal correlations and complexity together with conventional time-domain and frequency-domain HR variability analyses, were associated with depressive symptoms among HD patients. To our knowledge, this is the first study to investigate the association between depression and $\leq_2$. Moreover, no previous study has examined the association between depression and nonlinear properties of HR dynamics in a population of 100 subjects.

Age, gender, nutrition index, and diabetes are suggested to influence autonomic function and HR dynamics as well as mental states. To estimate the independent association between depression and HR dynamics and variability, we included those factors which might confound the results in the analysis. To explore the possibility of nonlinear relationships (such as J-curves) between these measures and depression, we compared depression severity among quintiles of HR dynamics and variability.

## METHODS

### Subjects

The subjects were recruited from the patients screened for the Nagoya Kidney Center (NKC) study between May 2001 and May 2002. The prospective NKC study was designed to explore the influence of psychosocial factors on the long-term prognosis of ESRD patients receiving chronic HD therapy. The protocol was approved by the Research Ethics Committee of Nagoya City University Graduate School of Medical Sciences, Japan. According to the selection criteria, the eligible individuals were ESRD patients receiving regular 4-hour HD therapy three times per week at the Nagoya Central Clinic, which is one of the three clinics involved in the NKC study in Japan. Individuals were also aged 70 years, could read and complete the self-administered questionnaire unaided, had not experienced episodes of acute myocardial infarction (AMI), stroke, or a major surgical procedure within the past 2 months, and had not experienced malignant neoplasm or any psychiatric diagnosis during the past 5 years. Patients were excluded if they had hemodynamically significant valvular or congenital heart disease, atrial fibrillation or flutter, high-grade heart block, or permanent pacemaker implantation. A trained research assistant interviewed the patients and confirmed whether they met the criteria and lacked cognitive impairments. Of the 379 patients registered, 249 met the criteria and were invited to participate in the study and complete the questionnaire. Among these 249 patients, 68 persons declined to participate; these individuals tended to be older and more likely to have physical problems than those who agreed to participate. An additional 14 patients were unable to participate because of their therapy schedules; four patients failed to complete the questionnaire due to their physical condition or for personal reasons. Hence, a total of 163 patients provided written informed consent and completed the questionnaire.

### Procedures

At enrollment, all patients underwent 24-hour Holter electrocardiographic analysis (Fukuda Denshi, Tokyo, Japan) and at the same time performed their usual daily activities. The participants were asked to complete a battery of questionnaires 1 week after the electrocardiographic examination. Blood chemistry results, a chest roentgenogram, and an echocardiogram obtained 1 month before the 24-hour electrocardiography (ECG) were used to assess the baseline clinical parameters. Medical data were obtained from hospital charts, including serum albumin concentration, protein catabolic rate (PCR) and Kt/V (a measure of HD treatment adequacy); these nutritional and dialytic parameters are established markers associated with survival in HD patients (27–30).

### Analysis of Holter Electrocardiograms

The Holter electrocardiograms were digitized with 12-bit resolution at 128 Hz, using a scanner (SCM2000, Fukuda Denshi), which detected and labeled all QRS complexes automatically. The results of the automatic analysis were reviewed, and any errors in QRS detection or labeling were edited manually. Based on the edited QRS labeling, patients with frequent ventricular and supraventricular ectopic beats that accounted for 10% of the total recorded beats were excluded. The normal-to-normal R-R interval data obtained from the edited time sequences of the QRS complexes were transferred onto a Microsoft Windows-based personal computer (8187CKJ, IBM, New York).

The computations of HR dynamics and variability measurements were performed by a custom-made Fortran 95 program. Subroutine source codes of the DFA were obtained from the website of Physio Toolkit (available at http://www.physionet.org), which is open-source software for biomedical science and engineering including nonlinear analysis of time series as well as conventional time-domain and frequency-domain HR variability analysis (31).

### Traditional Time-Domain and Frequency-Domain HR Variability Analysis

The time-domain and frequency-domain HR variability measurements were analyzed using the methods recommended by the Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology (5).

For time-domain HR variability, the mean normal-to-normal R-R intervals (mNN), standard deviation (SD) of the normal-to-normal R-R intervals (SDNN), and triangular index were calculated. For frequency-domain HR variability, the power spectrum was computed using a fast Fourier transformation and the following frequency bands: 0.0033 Hz (ultra-low frequency [ULF]); 0.0033 to 0.04 Hz (very-low frequency [VLF]); 0.04 to 0.15 Hz (low-frequency [LF]); and 0.15 to 0.4 Hz (high-frequency [HF]). The frequency-domain measurements of HR variability were transformed to natural logarithms because their distributions were skewed.

### Analysis of Nonlinear Dynamics

Nonlinear HR dynamics were assessed using DFA and ApEn. The DFA technique was used to quantify the fractal-like correlation properties of the R-R interval time series, and the details of this algorithm have been reported elsewhere (32). The scaling exponent indicates the strength of the correlations with previous values in the time series. Scaling exponent values approximating 0.5 suggest random dynamics (no correlation); values close to 1.5 describe highly correlated behavior; whereas values close to 1.0 are characteristic of fractal-like processes, suggesting that the fluctuations are generated by complex systems with multiple feedback regulations (13). The scaling exponents for HR dynamics were calculated separately for short-term (4–11 beats, $\leq_1$) and longer-term ( 11 beats, $\leq_2$) correlations.

ApEn is a measure that quantifies the unpredictability of fluctuations (16) and reflects the likelihood that similar patterns of observations will not be followed by additional similar observations. Smaller ApEn values imply a greater likelihood of this. If the time series is highly irregular, the occurrence of similar patterns will not be predictive for the following measurements, and ApEn will be larger. We computed ApEn according to the algorithm of Pincus (33) with a fixed set of parameters: m 2 and $r$ 20% of the SD of the data (m denotes the length of compared runs; r denotes the tolerance of the filter).

### Measure of Depression

The level of depressive symptoms was assessed using the Japanese version of the Beck Depression Inventory, Second Edition (BDI-II) (34).

TABLE 1. Pearson's Correlation Coefficient Between Heart Rate Dynamics and Variability Measures

| Variables | $\alpha_1$ | $\alpha_2$ | ApEn | mNN | SDNN | TI | HF | LF | VLF |
|---|---|---|---|---|---|---|---|---|---|
| HR dynamics measurements | | | | | | | | | |
| $\alpha_1$ | 1.00 | | | | | | | | |
| $\alpha_2$ | 0.54*** | 1.00 | | | | | | | |
| ApEn | 0.58*** | 0.55*** | 1.00 | | | | | | |
| Time-domain HRV measurements | | | | | | | | | |
| mNN (ms) | 0.01 | 0.10 | 0.35*** | 1.00 | | | | | |
| SDNN (ms) | 0.46*** | 0.28*** | 0.75*** | 0.32*** | 1.00 | | | | |
| TI | 0.43*** | 0.32*** | 0.76*** | 0.33*** | 0.91*** | 1.00 | | | |
| Frequency-domain HRV measurements | | | | | | | | | |
| HF log(ms$^2$) | 0.13 | 0.57*** | 0.57*** | 0.48*** | 0.56*** | 0.60*** | 1.00 | | |
| LF log(ms$^2$) | 0.69*** | 0.73*** | 0.75*** | 0.27* | 0.65*** | 0.65*** | 0.75*** | 1.00 | |
| VLF log(ms$^2$) | 0.67*** | 0.67*** | 0.83*** | 0.36*** | 0.74*** | 0.73*** | 0.74*** | 0.93*** | 1.00 |
| ULF log(ms$^2$) | 0.35*** | 0.18† | 0.70*** | 0.29* | 0.84*** | 0.77*** | 0.47*** | 0.53*** | 0.62*** |

*n* 119; $\alpha_1$ short-term scaling exponents; $\alpha_2$ long-term scaling exponents; ApEN approximate entropy; mNN mean normal-to-normal R-R intervals; SDNN standard deviation of normal-to-normal R-R intervals; TI triangular index; HF high-frequency band; LF low-frequency band; VLF very-low-frequency band; HRV heart rate variability.
† *p* .1; * *p* .05; *** *p* .001.

The BDI is a self-report tool that has been commonly used to evaluate depressive symptoms. Unique features of this inventory are its usefulness in screening for depression among the general population and measuring the severity of depression in clinical settings (35–37) and its application in ESRD patients (38,39). The original BDI was revised to correspond to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria in 1996, and was republished as the BDI-II. The version used in the current study has been translated into Japanese using the back-translation method and has been well validated in the general population (35) as well as in clinical settings (37). The BDI-II scores range from 0 to 63, and the cut-off score of 14 indicates at least a mild-to-moderate level of depression (34).

### Statistical Analysis

The data were analyzed using SPSS for Windows (version 12.0). All statistical tests were two-sided. A *p* .05 was considered to be statistically significant; *p* .10 and .05 were considered to be marginal.

To investigate the interrelationships among the HR variability measures as well as their linear associations with the BDI-II score and clinical markers, the Pearson's correlation coefficients between the variables were calculated.

The mean values of HR dynamics and variability measures and background characteristics were compared by gender (female/male), presence of diabetes (yes/no), and presence of depressive symptoms (BDI-II 14/ 14), using the $^2$ statistic for categorical variables and the Student's *t* test for continuous variables. Then, three-way analysis of covariance (ANCOVA) was conducted using the general linear model (GLM) (40). Gender, diabetes, and depression were entered as main factors; age and serum albumin concentration were included in the models as covariates. To explore the potential nonlinear associations between HR dynamics and variability measures and depression severity, the scores on the HR dynamics and variability measures were divided in quintiles for each subject. The mean differences in the BDI-II scores by subgroups, and according to the quintiles of HR dynamics and variability variables, were examined using the GLM. Tukey's post hoc tests were conducted successively.

## RESULTS

Of the 163 patients who completed the questionnaires, 19 patients did not undergo 24-hour ECG analysis during the study period, six failed to produce analyzable ECG data, and 15 were excluded because of atrial fibrillation or frequent ectopic beats ( 2000 per day). In addition, four patients were excluded because they had been prescribed antidepressants. Thus, data including HR dynamics and variability variables were analyzed for a total of 119 patients. There were no significant differences in age, gender, BDI-II scores, or medical history of diabetes among the subjects at the time of data completion.

### Correlations Between Variables

To explore the interrelationships between the HR dynamics and variability measures, Pearson's correlation coefficients were calculated (Table 1). Statistically significant correlations were observed between most of the HR dynamics and variability variables.

The linear associations of the HR dynamics and variability measures with depression score, age, and clinical indices are shown in Table 2. Age was negatively correlated with most of the HR dynamics and variability measures, but positively correlated with $\alpha_2$. HD duration failed to show significant correlations with any of the HR variables. All of the HR dynamics measurements as well as LF and VLF were significantly correlated with serum albumin concentration and PCR. The depression score was not associated with age or any of the clinical markers, but was significantly correlated with all of the HR dynamics measures and most of the HR variability indices. A significant positive correlation was detected between the depression score and $\alpha_2$.

### Comparisons by Gender

The demographic, clinical, and psychosocial characteristics of the subjects by gender are shown in Table 3. Women had significantly higher Kt/V and total cholesterol levels and were less likely to be current smokers. The variables that showed statistically significant or marginally significant gender differences were all HR dynamics measures: $\alpha_1$ (1.00 0.30 in women versus 1.15 0.27 in men, *p* .004), $\alpha_2$ (1.19 0.06 in women versus 1.16 0.06 in men, *p* .01), ApEn (0.81 0.26 in women versus 0.90 0.26 in men, *p* .09), HF (4.02 0.98 in women versus 4.15 0.98 in men, *p* .02), and LF (4.51 1.12 in women versus 5.05 1.32 in men,

**TABLE 2. Pearson's Correlation Coefficient Between Age, Medical Characteristics, BDI-II, Heart Rate Dynamics, and Variability Measures**

| Variables | Age (year) | Duration of Hemodialysis (year) | Serum Albumin (g/dl) | PCR (g/kg/day) | Kt/V | BDI-II |
|---|---|---|---|---|---|---|
| Depression score | | | | | | |
| BDI-II | 0.08 | 0.12 | 0.11 | 0.08 | 0.04 | |
| HR dynamics measurements | | | | | | |
| $\leq_1$ | 0.23* | 0.09 | 0.28* | 0.25* | 0.01 | 0.19* |
| $\leq_2$ | 0.36*** | 0.01 | 0.30* | 0.25* | 0.06 | 0.27* |
| ApEn | 0.16† | 0.04 | 0.23* | 0.20* | 0.05 | 0.21* |
| Time-domain HRV measurements | | | | | | |
| mNN (ms) | 0.15† | 0.06 | 0.05 | 0.03 | 0.22* | 0.04 |
| SDNN (ms) | 0.15† | 0.04 | 0.13 | 0.17† | 0.06 | 0.21* |
| TI | 0.15† | 0.04 | 0.11 | 0.26* | 0.11 | 0.16† |
| Frequency-domain HRV measurements | | | | | | |
| HF log(ms$^2$) | 0.19* | 0.02 | 0.15† | 0.07 | 0.12 | 0.25* |
| LF log(ms$^2$) | 0.27* | 0.04 | 0.28* | 0.22* | 0.07 | 0.31* |
| VLF log(ms$^2$) | 0.25* | 0.02 | 0.28* | 0.20* | 0.11 | 0.25* |
| ULF log(ms$^2$) | 0.02 | 0.11 | 0.01 | 0.14 | 0.06 | 0.17† |

*n* 119; BDI-II Beck Depression Inventory, Second Edition; PCR protein catabolic rate; Kt/V a measure of hemodialysis treatment adequacy; HR heart rate; $\leq_1$ short-term scaling exponents; $\leq_2$ long-term scaling exponents; ApEN approximate entropy; HRV heart rate variability; mNN mean normal-to-normal R-R intervals; SDNN standard deviation of normal-to-normal R-R intervals; TI triangular index; HF high-frequency band; LF low-frequency band; VLF very-low-frequency band; ULF ultra-low-frequency band.
† $p$ .1; * $p$ .05; *** $p$ .001.

**TABLE 3. Demographic, Clinical, and Psychosocial Characteristics of the Subjects**

| | Total *n* 119 | Men *n* 66 | Women *n* 53 | $p^a$ |
|---|---|---|---|---|
| Sociodemographic characteristics | | | | |
| Age (year) | 55.2 10.5 | 55.9 10.7 | 54.4 10.4 | .43 |
| Married (%) | 76.5% | 72.7% | 81.1% | .28 |
| Current smoker (%) | 24.6% | 38.5% | 7.5% | .001 |
| Clinical characteristics | | | | |
| Duration of HD (year) | 8.40 6.60 | 7.54 6.02 | 9.47 7.17 | .11 |
| Cause of ESRD (%) | | | | |
| Nephritis | 59.7% | 62.1% | 56.6% | .81 |
| Diabetes | 23.5% | 22.7% | 24.5% | |
| Others | 16.8% | 15.2% | 18.9% | |
| Depression severity | | | | |
| Total score of BDI-II | 13.4 8.84 | 13.0 8.71 | 13.8 9.05 | .61 |
| BDI-II 14 (%) | 41.2% | 45.5% | 35.8% | .29 |
| Laboratory measurements | | | | |
| PCR (g/kg/day) | 0.96 0.17 | 0.95 0.17 | 0.97 0.16 | .54 |
| Kt/V | 1.44 0.22 | 1.34 0.17 | 1.55 0.22 | .001 |
| Serum albumin concentration (g/dl) | 3.72 0.31 | 3.72 0.31 | 3.71 0.31 | .87 |
| Casual plasma blood glucose (mg/dl) | 98.2 37.7 | 98.0 33.1 | 98.5 43.1 | .95 |
| Total cholesterol (mg/dl) | 168.2 35.6 | 156.6 33.2 | 182.6 33.4 | .001 |
| Hematocrit (%) | 32.7 3.4 | 32.4 3.3 | 33.1 3.6 | .25 |
| Systolic blood pressure (mm Hg) | 150.9 21.1 | 152.7 19.8 | 148.7 22.6 | .31 |
| Left ventricular ejection fraction (%) | 0.66 0.10 | 0.67 0.09 | 0.65 0.11 | .57 |
| Having coronary revascularization (%) | 5.9% | 6.2% | 5.7% | .91 |
| $\geq$ blockade (%) | 16.8% | 22.7% | 9.4% | .05 |
| Calcium blockade (%) | 58.8% | 62.1% | 54.7% | .42 |

HD hemodialysis; ESRD end-stage renal disease; BDI-II Beck Depression Inventory, Second Edition; PCR protein catabolic rate; Kt/V a measure of hemodialysis treatment adequacy.
Values are mean standard deviation or %.
[a] Tests of significance by unpaired *t* tests for continuous variables and $^2$ tests for categorical variables.

**TABLE 4. Comparisons of Heart Rate Dynamics and Variability Measures by Depression, Diabetes and Gender With Adjustment for Age and Serum Albumin Concentration Among Patients With ESRD**

| | Depression | | | | | Diabetes | | | | | Sex | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | BDI-II 14 | | BDI-II 14 | | $p$ | Non-DM | | DM | | $p$ | Men | | Women | | $p$ |
| | $n$ 70 | | $n$ 49 | | | $n$ 92 | | $n$ 27 | | | $n$ 66 | | $n$ 53 | | |
| HR dynamics measurements | | | | | | | | | | | | | | | |
| $\alpha_1$ | 1.03 | 0.04 | 0.97 | 0.04 | .34 | 1.12 | 0.03 | 0.88 | 0.05 | .001 | 1.07 | 0.04 | 0.93 | 0.04 | .01 |
| $\alpha_2$ | 1.18 | 0.01 | 1.20 | 0.01 | .09 | 1.17 | 0.01 | 1.21 | 0.01 | .006 | 1.17 | 0.01 | 1.21 | 0.01 | .006 |
| ApEn | 0.85 | 0.04 | 0.79 | 0.04 | .33 | 0.88 | 0.03 | 0.76 | 0.05 | .05 | 0.88 | 0.04 | 0.77 | 0.04 | .06 |
| Time-domain HRV measurements | | | | | | | | | | | | | | | |
| mNN (ms) | 792.8 | 16.8 | 787.3 | 17.0 | .82 | 797.5 | 12.1 | 782.6 | 20.6 | .53 | 796.2 | 15.8 | 783.9 | 18.1 | .61 |
| SDNN (ms) | Significant gender interaction. See Table 5. | | | | | | | | | | | | | | |
| TI | 25.6 | 1.7 | 24.4 | 1.7 | .60 | 28.2 | 1.2 | 21.7 | 2.1 | .007 | 25.4 | 1.6 | 24.5 | 1.8 | .72 |
| Frequency-domain HRV measurements | | | | | | | | | | | | | | | |
| HF log(ms$^2$) | Significant gender interaction. See Table 5. | | | | | | | | | | | | | | |
| LF log(ms$^2$) | | | | | | | | | | | | | | | |
| VLF log(ms$^2$) | | | | | | | | | | | | | | | |
| ULF log(ms$^2$) | | | | | | | | | | | | | | | |

ESRD end-stage renal disease; BDI-II Beck Depression Inventory, second edition; DM diabetes mellitus; $\alpha_1$ short-term scaling exponents; $\alpha_2$ long-term scaling exponents; ApEN approximate entropy; HRV heart rate variability; mNN mean normal-to-normal R-R intervals; SDNN standard deviation of normal-to-normal R-R intervals; TI triangular index; HF high-frequency band; LF low-frequency band; VLF very-low-frequency band; ULF ultra-low-frequency band.

Values are estimated mean standard error by three-way (depression diabetes gender) analysis of covariance with adjustment for age and serum albumin concentration.

$p$ .02). There was no significant gender difference in any of the time-domain measures.

### Comparisons by Diabetes

Diabetic patients were more depressed (total BDI-II 17.4 11.5 versus 12.1 7.5, $p$ .03), had spent fewer years undergoing dialysis (3.4 2.2 versus 9.9 6.7 years, $p$ .001), had lower Kt/V values (1.32 0.22 versus 1.47 0.21, $p$ .003), were more likely to have undergone revascularization (17.9% versus 2.2%, $p$ .002), and were more likely to have been prescribed calcium blockers (75.0% versus 53.8%, $p$ .047) than nondiabetics. Most of the HR variables showed statistically significant differences according to the presence of diabetes, except for the mNN. The $\alpha_2$ was significantly higher in diabetics, whereas the other variables were significantly lower in diabetics than in nondiabetics.

### Comparisons by Depression

The depressed patients were marginally less likely to be married (67.3% versus 82.9%, $p$ .05). There were no other statistically significant differences in age, gender, smoking habits, or clinical characteristics associated with the presence or absence of depressive symptoms. Among HR dynamics and variability measures, only LF showed a significant difference by depressive status. Depressed patients had a lower LF (4.5 1.4) than nondepressed patients (5.0 1.1, $p$ .03). Although there were no statistically significant differences in the other variables, they all tended to be lower in the depressed group than the nondepressed group, with the exception of the $\alpha_2$. The $\alpha_2$ values were slightly higher in the depressed than the nondepressed group.

### Comparisons by Gender Diabetes Depression

To examine the independent association between HR dynamics and variability measures and depression, three-way (gender diabetes depression) ANCOVAs with adjustments for age and serum albumin concentrations were conducted. Table 4 presents the adjusted means, standard errors, and $p$ values. As a significant gender diabetes interaction was observed in SDNN, and gender depression interactions were confirmed in frequency-domain indices, these variables were analyzed separately by gender using two-way ANCOVA (depression diabetes) (Table 5). No significant three-way interaction was observed for any measure.

HR dynamics measures showed independent susceptibility to diabetes and gender, respectively; $\alpha_1$ and ApEn were significantly or marginally significantly higher in diabetics and in men, whereas $\alpha_2$ was significantly lower in these subject groups. Regardless of gender and diabetes, $\alpha_2$ showed marginally significant differences in depression, such that depressed patients had a higher $\alpha_2$ than nondepressed patients.

In men, all four frequency-domain indices were significantly or marginally significantly lower in depressed patients than in nondepressed patients, even after adjusting for diabetes and other covariates (Table 5). By contrast, no significant difference was observed in any of the HR variability factors by depression in women.

TABLE 5. Comparisons of SDNN and Frequency-Domain Heart Rate Variability Measures by Depression and Diabetes With Adjustment for Age and Serum Albumin Concentration Among ESRD Patients by Gender

| | Non-DM | | | | DM | | | | *p* | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Nondepressed BDI-II 14 | | Depressed BDI-II 14 | | Nondepressed BDI-II 14 | | Depressed BDI-II 14 | | Depressed Versus Nondepressed | DM Versus Non-DM |
| Men | *n* | 28 | *n* | 23 | *n* | 8 | *n* | 7 | | |
| SDNN (ms) | 108.0 | 6.0 | 96.1 | 6.7 | 97.0 | 11.3 | 87.3 | 12.2 | .26 | .30 |
| HF log(ms$^2$) | 4.31 | 0.17 | 3.95 | 0.19 | 4.68 | 0.32 | 3.57 | 0.35 | .009 | .98 |
| LF log(ms$^2$) | 5.47 | 0.22 | 4.92 | 0.25 | 5.12 | 0.42 | 3.76 | 0.45 | .008 | .03 |
| VLF log(ms$^2$) | 6.76 | 0.18 | 6.33 | 0.20 | 6.55 | 0.33 | 5.71 | 0.36 | .03 | .15 |
| ULF log(ms$^2$) | 9.26 | 0.18 | 8.69 | 0.20 | 8.81 | 0.35 | 8.27 | 0.37 | .06 | .14 |
| Women | *n* | 29 | *n* | 11 | *n* | 5 | *n* | 8 | | |
| SDNN (ms) | 101.5 | 6.7 | 107.0 | 10.8 | 66.1 | 16.4 | 71.0 | 12.7 | .67 | .005 |
| HF log(ms$^2$) | 4.12 | 0.18 | 4.45 | 0.29 | 3.33 | 0.44 | 3.53 | 0.34 | .42 | .01 |
| LF log(ms$^2$) | 4.83 | 0.18 | 4.78 | 0.29 | 3.51 | 0.44 | 3.63 | 0.34 | .92 | .001 |
| VLF log(ms$^2$) | 6.20 | 0.17 | 6.31 | 0.28 | 5.04 | 0.43 | 5.54 | 0.33 | .33 | .004 |
| ULF log(ms$^2$) | 8.65 | 0.22 | 9.12 | 0.36 | 8.05 | 0.54 | 8.19 | 0.42 | .46 | .06 |

SDNN standard deviation of normal-to-normal R-R intervals; ESRD end-stage renal disease; DM diabetes mellitus; BDI-II Beck Depression Inventory, Second Edition; HF high-frequency band; LF low-frequency band; VLF very-low-frequency band; ULF ultra-low-frequency band.
Values are estimated mean standard error by two-way (depression * diabetes) analysis of covariance with adjustment for age and serum albumin concentration.

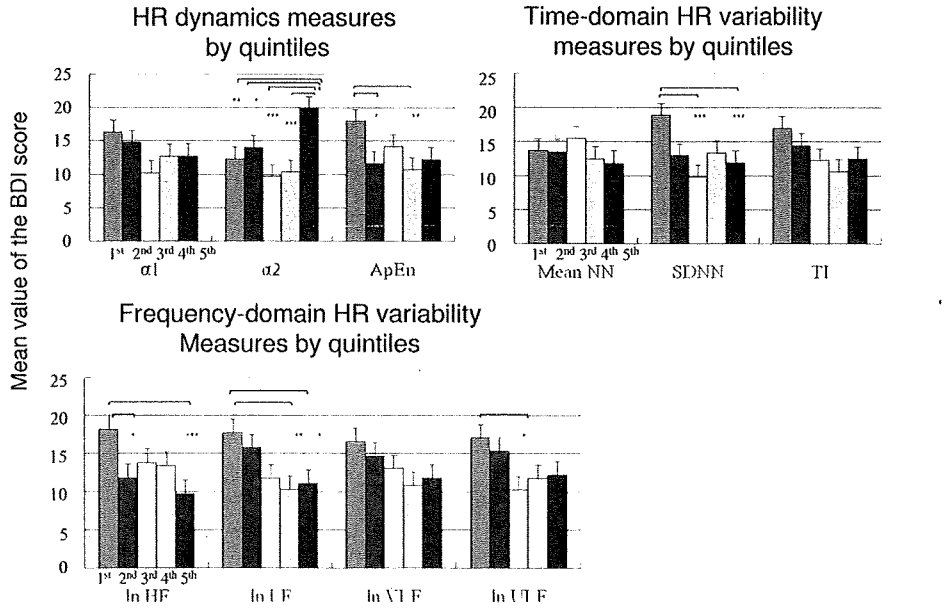


Figure 1. Mean BDI-II scores with standard errors for the quintiles of the nonlinear and traditional HR variability measures. ANOVA tests showed significant overall differences in $\leq_2$, ApEn, SDNN, HF, and LF, and a marginal difference in ULF. Statistically significant differences between quintiles confirmed by Tukey's post hoc test are indicated as *$p$ .05, **$p$ .01, and ***$p$ .001. BDI-II Beck Depression Inventory, Second Edition; HR heart rate; ANOVA analysis of variance; $\leq_2$ the long-term scaling exponent; ApEn approximate entropy; SDNN standard deviation of normal-to-normal R-R intervals HF high-frequency band; LF low-frequency band; ULF ultra-low-frequency band.

### Depression by Quintiles of HR Dynamics and Variability Measures

To explore the nonlinear associations between depression severity and the levels of HR dynamics and variability measurement values, we examined the mean BDI-II scores for the quintiles of the HR dynamics and variability measures using the GLM (Figure 1). With the exception of $\leq_2$, the members of the lowest quintiles of the HR dynamics and variability measures showed the highest average depression scores compared with other subjects. In $\leq_2$, the highest quintile showed the highest depression scores, and those in the middle quintile showed the lowest depression scores.

## DISCUSSION

This study confirmed that the fractal and complexity properties of HR dynamics, as well as conventional time-domain and frequency-domain measures of HR variability, tend to be associated with depression severity among ESRD patients.

Low HR variability measured by conventional methods has been associated with depression in many studies of patients with CHD (4). Reduced HR variability, as measured by conventional methods, is thought to mainly reflect excessive sympathetic and/or inadequate parasympathetic tones. However, cardiac regulations are determined by complex interactions of hemodynamic, electrophysiological, and humoral variables as well as by autonomic and central nervous regulation (5). HR dynamics indices are expected to reflect the capacity of physiologic systems to respond to unpredictable stress and stimuli, and to describe the total individual soundness of physiological regulatory systems. The present results suggest that depressed patients are not merely in a state where autonomic nervous systems are disrupted, but rather they experience a broader dysregulation of physiological systems. Further evidence, including the analysis of various background correlates and experimental studies, will be necessary to disclose the mechanisms of the associations between depression and HR dynamics and variability.

The association between $\leq_2$ and depression has not previously been examined. Earlier we reported adverse effects of both high and low values of $\leq_2$ on cardiac death rates among 81 HD patients with coronary artery disease (22). In our present study, we confirmed a J-curve relationship between $\leq_2$ and depression severity. Theoretically, reduced exponent values indicate random dynamics (that is, no correlation), whereas increased values describe highly correlated HR behaviors (32). Therefore, it seems reasonable that the favorable level of $\leq_2$ in relationship to depression lies in the middle range. Although it is not possible to further discuss the extent to which depression explains the associations between $\leq_2$ and cardiac deaths from the available data, ongoing prospective studies will disclose the linkage or independent influences of depression and HR dynamics on the prognosis of this population.

In relationship to depression severity, similar trends were observed in $\leq_1$ and ApEn in the present subjects; the lowest depression scores were not apparent in the lowest or highest quintiles, but rather in the third or the fourth. Only one previous study has reported an association between depression and $\leq_1$ and ApEn (26). This study found that in patients 60 years of age with recent unstable angina pectoris or AMI ($n$ 52, women 52%), $\leq_1$ was positively correlated ($r$ .31, $p$ .02) and ApEn was negatively correlated ($r$ .28, $p$ .046) with the total score of the Hamilton Depression Scale (41). HR dynamics is influenced by aging, gender, and various physiological factors (42). Therefore, the inconsistency between these previous results and our own might be partly explained by differences in background characteristics. It is also possible that simple dichotomization of the variables might offset the effects of high and low values and yield misleading results. The possible nonlinear associations with health indices and HR dynamics should be examined carefully to establish favorable ranges for positive health outcomes.

Aging, gender, and physical disorders such as severe heart failure have previously been suggested to influence HR dynamics (42), although their interactions have not been investigated. We confirmed that the influences of gender and diabetes on HR dynamics were independent of each other as well as depression. Frequency-domain indices revealed significant gender interactions with depression or/and with diabetes. In men, frequency-domain indices were altered by depression, but only the LF was altered by diabetes. Low LF was independently associated with depression and diabetes in men. By contrast, depression failed to show a significant association with any frequency-domain indices in women, whereas clear differences were associated with diabetes. From the present results, however, it is not possible to conclude that men are more sensitive to depression than women in relationship to frequency-domain HR variability. According to the evidence from a cohort of 500,868 diabetic patients in Taiwan, female patients were suggested to be more vulnerable to autonomic neuropathy than male patients (43). In addition, the influence of the menstrual cycle on HR variability indices has been suggested (44,45). One previous study reported gender influences on fractal dynamics and the complexity of HR dynamics including $\leq_2$ (46). Significant gender differences were not found in $\leq_2$, whereas values of $\leq_1$ and conventional HR variability measures were significantly higher and ApEn was lower in men among the healthy population (46). The possible interactions between gender, age, and physiological factors need to be considered to clarify the properties of HR dynamics and variability measurements.

Our current study had some limitations. First, our subjects were ESRD patients aged 70 years, who received HD therapy without severe physical problems and who could complete the questionnaire unaided. So, our study group was healthier than the general HD patient population. Moreover, we excluded those who had received a psychiatric diagnosis to avoid the influence of psychotropic medications (47–49). Severely depressed patients were not included, which might explain why we failed to observe significant differences in $\leq_1$ and ApEn in the presence of depressive symptoms.

Second, we used self-report measures to evaluate depression. Depressed patients can have a distorted cognitive style and perceive themselves negatively (50). This would overestimate depressive symptoms, thus attenuating the association between depression and HR variables. Depressed patients often complain of physical symptoms as well as emotional disturbances, and it is especially difficult for patients suffering from chronic diseases to distinguish them. The depression score might therefore only reflect a patient's somatic disease severity, which invites a loss of HR dynamics and reduced HR variability. We compared the correlation coefficient between HR dynamics and variability measures and the two subscales of BDI-II, namely, the somatic-affective and the cognitive subscales (34). However, no differences were apparent (data not shown).

Third, depression as defined in the present study was not equivalent to major depression as defined by the DSM criteria. Thus, although the BDI has been well validated and used to measure depression severity in a number of studies of ESRD

patients, our findings should be verified using different measurement tools.

In conclusion, loss of fractal HR dynamics and reduced HR variability measures are associated with depression in ESRD patients undergoing HD therapy. To confirm an association between depression and altered HR dynamics or their independent influences on prognosis, further studies with a prospective design will be necessary. Our findings should also be validated by examining other populations with different backgrounds.

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