TABLE 2

**Successful reproductive outcome after examination of uterine anomalies in patients with recurrent miscarriage.**

| | Success rate per pregnancy | | | | | | Cumulative success rate | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | With anomalies (n = 42) | Bicornuate | Septum | Without anomalies (n = 1528) | Difference in % | *P* value | With anomalies (n = 41)[a] | Without anomalies (n = 1528) | Difference in % | *P* value |
| Pregnancy after the ascertainment of uterine anomaly | | | | | | | | | | |
| First | 25/42 (59.5)[b] | 21/37 (56.8) | 4/5 (80.0) | 1096/1528 (71.7) | −12.2 | .084 | 25 (61.0) | 1096 (71.7) | −10.7 | .133 |
| Second | 5/9 (55.6) | 4/8 (50.0) | 2/2 (100) | 166/275 (60.4)[c] | −4.8 | .772 | 30 (73.2) | 1262 (82.6) | −9.4 | .119 |
| Third | 2/2 (100) | 2/2 (100) | | 38/69 (55.0) | +45.0 | .207 | 32 (78.0) | 1300 (85.1) | −7.1 | .215 |
| Fourth | | | | 4/18 (22.2) | | | | 1304 (85.3) | | |
| Fifth | | | | 3/9 (33.3) | | | | 1307 (85.5) | | |
| Sixth | | | | 0/6 (0) | | | | 1307 (85.5) | | |
| Final follow up | | | | | | | 32 (78.0) | 1307 (85.5) | −7.5 | |

*Note:* Values are numbers (percentages) of couples. Success rate is defined as the live birth.

[a] One case underwent surgery between the first and second pregnancy after the ascertainment of an anomaly, thus this case was excluded from the cumulative analysis.

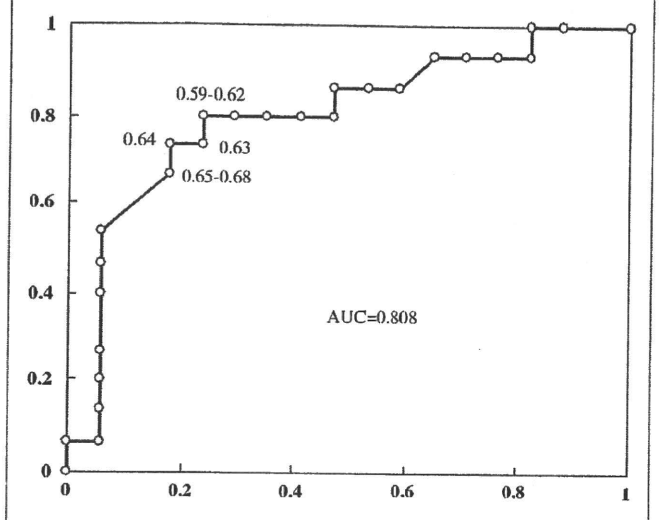
[b] Comparison was performed between patients both with anomalies and with normal uterus.

[c] Cases who could succeed in the first pregnancy were excluded from the analysis of the second and subsequent pregnancies.

*Sugiura-Ogasawara. Uterine anomaly and recurrent miscarriage. Fertil Steril 2010.*

**FIGURE 1**

ROC analysis of D/C ratio.




*Sugiura-Ogasawara. Uterine anomaly and recurrent miscarriage. Fertil Steril 2010.*

cumulative live-birth rate after one or two metroplasties was 54.3% (51 of 94). Both live-birth rates were lower than that without surgery in the present study. The benefits of surgical correction (open and hysteroscopic) on pregnancy outcome have yet to be assessed in a randomized trial, but the D/C ratio might be useful in deciding who should be selected.

## Limitations

In the present study, clear uterine malformations such as septate, bicornuate, or unicornuate uterus and didelphys were found in 3.2% of patients. The prevalence of clear congenital uterine anomalies in patients with a history of recurrent miscarriages has been reported to be 1.8%–20.1% with the arcuate uterus excluded (5–7) and thus higher than the 2.2% documented for fertile women (28 of 1289) (2). Minor malformations like arcuate uterus do not appear to have any impact on reproduction (2), and therefore we here excluded cases with this anomaly.

HSG is the diagnostic modality that has most often led to a tentative diagnosis of congenital anomalies (19), but when used alone it cannot distinguish between a septate and a bicornuate uterus. Thus laparoscopy has hitherto been needed for a final diagnosis. The advent of sonohysterography, MRI (20), and 3D ultrasound now allows for accurate differential diagnosis (21), although distinguishing an arcuate from a mildly subseptate or bicornuate uterus still remains difficult.

It is important to distinguish between the bicornuate uterus and the septate uterus, especially regarding the selection of surgical methods because TCR should not be performed for the former. We here ascertained the type of anomaly to study the prevalence in accordance with the American Fertility Society classification of Mullerian anomalies. Woelfer et al. proved new 3D criteria by which a bicornuate uerus can be distinguished from a septate uterus when a fundal indentation >10 mm dividing the two cornua is detectable (21). Using 3D ultrasound, it has been found that the septate uterus has the higher incidence. The criteria are useful before deciding on using TCR for the septum. It is difficult to examine the significance of the distinction between bicornuate and septate uteri because of the absence of internationally established criteria, although we have given the live-birth rate for each anomaly in Table 2. Thus we focused not on type of anomalies but rather on the D/C ratio. In addition, the sample size in the anomaly group was too small to allow any conclusion when we distinguished between the two groups.

While we examined 1676 patients who became pregnant at least one time in the present study, we failed to follow up all those who received systemic examination for causes of recurrent miscarriage at our hospital because some lived at a long distance. Some patients might become infertile after miscarriage. A prospective case-control study should therefore be conducted to compare live-birth rates between patients with and without surgery, including consideration of the infertile rate.

## Conclusion

Congenital uterine anomalies have a negative impact on reproductive outcome in couples with recurrent miscarriage, being particularly associated with normal embryonic karyotype miscarriages. The height of the defect/length of the remaining uterine cavity ratio, the D/C ratio, has independent predictive value for further miscarriage in recurrent cases. Comparison of cases of anomalies with and without surgery is needed in future recurrent miscarriage studies.

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# BMI and All-cause Mortality Among Japanese Older Adults: Findings From the Japan Collaborative Cohort Study

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**The association between BMI and all-cause mortality may vary with gender, age, and ethnic groups. However, few prospective cohort studies have reported the relationship in older Asian populations. We evaluated the association between BMI and all-cause mortality in a cohort comprised 26,747 Japanese subjects aged 65–79 years at baseline (1988–1990). The study participants were followed for an average of 11.2 years. Proportional-hazards regression models were used to estimate mortality hazard ratios (HRs) and 95% confidence intervals. Until 2003, 9,256 deaths occurred. The underweight group was associated with a statistically higher risk of all-cause mortality compared with the mid-normal-range group (BMI: 20.0–22.9); resulting in a 1.78-fold (95% confidence interval: 1.45–2.20) and 2.55-fold (2.13–3.05) increase in mortality risk among severest thin men and women (BMI: <16.0), respectively. Even within the normal-range group, the lower normal-range group (BMI: 18.5–19.9) showed a statistically elevated risk. In contrast, being neither overweight (BMI: 25.0–29.9) nor obese (BMI: ≥30.0) elevated the risk among men; however among women, HR was slightly elevated in the obese group but not in the overweight group compared with the mid-normal-range group. Among Japanese older adults, a low BMI was associated with increased risk of all-cause mortality, even among those with a lower normal BMI range. The wide range of BMI between 20.0 and 29.9 in both older men and women showed the lowest all-cause mortality risk.**

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## INTRODUCTION

The relationship between high BMI (BMI: weight in kg/height in $m^2$) and all-cause mortality is well known (1,2). The World Health Organization defines overweight as a BMI of 25.0–29.9 $kg/m^2$ and obesity as a BMI of ≥30 $kg/m^2$. These BMI thresholds have been recommended worldwide for all individuals aged ≥18 (3). However, increasing evidence suggests that the association between BMI and mortality varies with age. A 2007 review by Janssen and Mark concluded that BMIs in the overweight range (BMI: 25.0–29.9) were not associated with a significant increase in mortality risk among the older adults (4). Furthermore, some recent studies have revealed that among this age group, being underweight seems to be a better predictor of mortality than obesity (5–7). Thus, it remains to be established whether older adults require different BMI cut-off points from those younger.

Japan has witnessed a rapid growth in its older population in recent years. From a public health perspective, it is important to determine the BMI range associated with a low mortality risk for them. We sought to examine the association between BMI and all-cause mortality among participants in our Japan Collaborative Cohort study.

## METHODS AND PROCEDURES

### Study subjects and data collection

The study design and methods adopted by the Japan Collaborative Cohort study have been previously described elsewhere (8,9). Briefly, from 1988 to 1990, healthy subjects in 45 areas throughout Japan replied to a self-administered questionnaire. The cohort comprised 110,792 subjects aged 40–79 years old at baseline, among whom those participants aged 65–79 years were enrolled in this study. The ethical board of the Nagoya University School of Medicine, where the central office of the Japan Collaborative Cohort study was located, has approved our complete study design.

### Follow-up

The cause and date of death of the study subjects were identified by reviewing all death certificates in each area by each area investigator

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with the permission of the Director-General of the Prime Minister's Office (Ministry of Internal Affairs and Communications). Those who had moved out of a study area were treated as censored. Follow-ups were conducted to the end of 2003, except in four areas where they were discontinued at the end of 1999.

### BMI

Information on height and weight as well as lifestyle variables was gathered from self-administered questionnaires. BMI at baseline was calculated based on the height and weight reported. We grouped subjects into the following nine detailed categories according to the World Health Organization classification (10): BMIs <16.0, 16.0–16.9, 17.0–18.4, 18.5–19.9, 20.0–22.9, 23.0–24.9, 25.0–27.4, 27.5–29.9, and ≥30.0. These categories incorporated the current definitions of underweight (BMI: <18.5), normal range (18.5–24.9), overweight (25.0–29.9), and obese (≥30.0) (3). There were 26,747 subjects (11,230 men and 15,517 women) aged 65–79 years who provided information on BMI, all of whom were considered to be eligible for this study.

### Analysis

To compare the proportions of subject characteristics across BMI categories at baseline, we used the Mantel–Haenszel test. Hazard ratios (HRs) were calculated separately by gender according to Cox's proportional hazard model. Not only in all the subjects combined but also in subcohorts of noncurrent smokers, physically active subjects (engaging in physical exercise ≥1 h per week and/or walking >1 h/day), and those

**Table 1 Distribution of some demographic factors according to BMI categories**

| | | BMI category | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | <16.0 | 16.0–16.9 | 17.0–18.4 | 18.5–19.9 | 20.0–22.9 | 23.0–24.9 | 25.0–27.4 | 27.5–29.9 | ≥30.0 |
| Men | | | | | | | | | | |
| Age at baseline | | | | | | | | | | |
| 65–69 | % | 19.0 | 31.0 | 36.5 | 43.8 | 47.4 | 49.5 | 52.7 | 51.6 | 50.6*** |
| 70–74 | % | 34.1 | 30.6 | 37.4 | 32.8 | 32.1 | 32.5 | 32.8 | 31.2 | 28.6 |
| 75–79 | % | 46.8 | 38.4 | 26.1 | 23.4 | 20.5 | 18.0 | 14.4 | 17.2 | 20.8 |
| Current cigarette smoker | % | 50.8 | 48.7 | 52.8 | 47.2 | 42.6 | 34.3 | 34.2 | 30.8 | 29.9*** |
| Current alcohol drinker | % | 44.4 | 53.9 | 56.5 | 60.7 | 62.0 | 61.4 | 61.8 | 66.7 | 50.6*** |
| Sleep 6.5–8.4 h/day | % | 49.2 | 57.3 | 54.0 | 57.4 | 59.8 | 60.8 | 57.7 | 54.8 | 48.1* |
| Physically active | % | 42.9 | 47.4 | 46.7 | 48.9 | 49.6 | 47.6 | 44.8 | 40.9 | 42.9 |
| College or higher education | % | 11.1 | 12.1 | 11.9 | 12.6 | 13.6 | 14.6 | 14.8 | 12.2 | 9.1 |
| High-mental stress | % | 7.9 | 13.8 | 9.8 | 8.7 | 7.8 | 8.6 | 7.7 | 10.0 | 11.7* |
| Married | % | 66.7 | 75.9 | 70.6 | 72.6 | 73.7 | 76.4 | 77.3 | 80.3 | 75.3* |
| Eating green vegetables almost daily | % | 23.0 | 31.0 | 28.1 | 30.8 | 29.3 | 28.8 | 27.8 | 23.7 | 15.6* |
| No prior disease history (cancer, MI, or stroke) | % | 46.0 | 59.5 | 59.5 | 62.7 | 65.8 | 63.3 | 64.8 | 62.7 | 66.2*** |
| Number | | 126 | 232 | 871 | 1,622 | 4,670 | 2,217 | 1,136 | 279 | 77 |
| Women | | | | | | | | | | |
| Age at baseline | | | | | | | | | | |
| 65–69 | % | 28.1 | 41.7 | 43.0 | 45.4 | 50.0 | 54.5 | 56.7 | 58.2 | 53.2*** |
| 70–74 | % | 37.6 | 32.8 | 33.4 | 31.8 | 31.3 | 29.8 | 29.2 | 28.6 | 28.4 |
| 75–79 | % | 34.3 | 25.5 | 23.5 | 22.9 | 18.7 | 15.7 | 14.1 | 13.2 | 18.4 |
| Current cigarette smoker | % | 7.9 | 9.0 | 6.0 | 4.7 | 3.6 | 3.5 | 3.8 | 5.6 | 5.1*** |
| Current alcohol drinker | % | 11.6 | 14.2 | 16.3 | 16.3 | 16.3 | 17.7 | 15.9 | 18.1 | 15.1 |
| Sleep 6.5–8.4 h/day | % | 50.0 | 54.2 | 55.6 | 54.7 | 58.0 | 56.0 | 56.6 | 53.3 | 54.7* |
| Physically active | % | 29.8 | 40.9 | 42.4 | 43.7 | 45.4 | 44.0 | 42.9 | 38.9 | 35.0*** |
| College or higher education | % | 9.5 | 4.9 | 6.8 | 6.2 | 6.2 | 5.6 | 5.0 | 3.8 | 4.2*** |
| High-mental stress | % | 14.5 | 7.5 | 10.4 | 9.4 | 8.9 | 10.3 | 9.6 | 9.2 | 11.2* |
| Married | % | 43.8 | 43.5 | 54.8 | 51.8 | 52.2 | 53.0 | 53.4 | 53.6 | 51.7** |
| Eating green vegetables almost daily | % | 24.4 | 33.3 | 30.9 | 33.0 | 32.1 | 32.2 | 31.6 | 30.6 | 34.4 |
| No prior disease history (cancer, MI, or stroke) | % | 61.2 | 61.4 | 63.1 | 64.1 | 65.4 | 64.1 | 66.3 | 65.4 | 55.9 |
| Number | | 242 | 345 | 1,062 | 1,832 | 5,596 | 3,107 | 2,234 | 768 | 331 |

MI, myocardial infarction.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ by Mantel–Haenszel test adjusting for age categories.

without a disease history of cancer, myocardial infarction and/or stroke were analyzed because these factors were known to influence both BMI and mortality (11–14). In addition to age-adjusted HRs, we calculated HRs adjusting for the following potential confounding factors: smoking (current smoker, exsmoker, nonsmoker, or unknown), alcohol consumption (current drinker, exdrinker, nondrinker, or unknown), sleep duration per night (<6.4 h, 6.5–8.4 h, ≥8.5 h, or unknown), physical activity (engaging in physical exercise ≥1 h per week and/or walking >1 h/day, others or unknown), education (attended school up to 15 years of age, 18 years, >18 years or unknown), perceived stress (yes, no, or unknown), marital status (married, single, or unknown), frequency of green vegetables consumed (almost daily, not daily, or unknown), and history of cancer, myocardial infarction or stroke (yes, no, or unknown). Those potential confounding factors were queried in a self-administered questionnaire, and the results of validation studies on the physical activity and food frequency questionnaire were reported previously (15,16). Moreover, additional analyses were conducted to exclude those subjects whose events occurred within 3 years after baseline to avoid reverse-causality bias.

We used the SAS program version 9.1 (SAS Institute, Cary, NC) for analyses conducted at the Aichi Medical University Computation Center.

## RESULTS

Mean value of BMI was 21.9 among men and 22.5 among women. Proportions of those underweight (BMI: <18.5), overweight (BMI: 25.0–29.9) and obese (BMI: ≥30.0) were 10.9, 12.6, and 0.7% among men, and 10.6, 19.3, and 2.1% among women at baseline, respectively. Compared to those with normal-range BMI, both underweight and overweight/obese men and women were less likely to be drinkers, to sleep for the normal duration, and to be physically active, while they were more likely to suffer from high levels of mental stress (Table 1). Underweight and overweight/obese men were less likely to eat green vegetables, and corresponding women were more likely to be current smokers. However, among men, the proportion of current smokers decreased with increasing BMI. Among both men and women, subjects who were young, married, and free from prior disease history (cancer, myocardial infarction, or stroke) increased according to increasing BMI. Highly educated subjects showed different trends by gender,

**Table 2 Cause of mortality according to BMI categories**

| | BMI category | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | <16.0 | 16.0–16.9 | 17.0–18.4 | 18.5–19.9 | 20.0–22.9 | 23.0–24.9 | 25.0–27.4 | 27.5–29.9 | ≥30.0 | Total |
| Men | | | | | | | | | | |
| Number at baseline | 126 | 232 | 871 | 1,622 | 4,670 | 2,217 | 1,136 | 279 | 77 | 11,230 |
| Number of deaths | | | | | | | | | | |
| All causes | 94 | 157 | 500 | 831 | 2,149 | 936 | 473 | 115 | 37 | 5,292 |
| % | 74.6 | 67.7 | 57.4 | 51.2 | 46.0 | 42.2 | 41.6 | 41.2 | 48.1 | 47.1 |
| Malignant neoplasms | 13 | 42 | 139 | 252 | 762 | 320 | 151 | 35 | 11 | 1,725 |
| %[a] | 13.8 | 26.8 | 27.8 | 30.3 | 35.5 | 34.2 | 31.9 | 30.4 | 29.7 | 32.6 |
| Diseases of the circulatory system | 23 | 31 | 150 | 244 | 681 | 329 | 179 | 44 | 15 | 1,696 |
| %[a] | 24.5 | 19.7 | 30.0 | 29.4 | 31.7 | 35.1 | 37.8 | 38.3 | 40.5 | 32.0 |
| Pneumonia | 18 | 27 | 63 | 98 | 219 | 73 | 33 | 9 | 5 | 545 |
| %[a] | 19.1 | 17.2 | 12.6 | 11.8 | 10.2 | 7.8 | 7.0 | 7.8 | 13.5 | 10.3 |
| Senility | 3 | 2 | 17 | 16 | 40 | 10 | 6 | 0 | 1 | 95 |
| %[a] | 3.2 | 1.3 | 3.4 | 1.9 | 1.9 | 1.1 | 1.3 | 0.0 | 2.7 | 1.8 |
| Women | | | | | | | | | | |
| Number at baseline | 242 | 345 | 1,062 | 1,832 | 5,596 | 3,107 | 2,234 | 768 | 331 | 15,517 |
| Number of deaths | | | | | | | | | | |
| All causes | 132 | 121 | 362 | 536 | 1,322 | 690 | 519 | 179 | 103 | 3,964 |
| % | 54.5 | 35.1 | 34.1 | 29.3 | 23.6 | 22.2 | 23.2 | 23.3 | 31.1 | 25.5 |
| Malignant neoplasms | 21 | 26 | 65 | 132 | 359 | 213 | 161 | 45 | 24 | 1,046 |
| %[a] | 15.9 | 21.5 | 18.0 | 24.6 | 27.2 | 30.9 | 31.0 | 25.1 | 23.3 | 26.4 |
| Diseases of the circulatory system | 48 | 42 | 151 | 210 | 488 | 272 | 199 | 87 | 48 | 1,545 |
| %[a] | 36.4 | 34.7 | 41.7 | 39.2 | 36.9 | 39.4 | 38.3 | 48.6 | 46.6 | 39.0 |
| Pneumonia | 17 | 17 | 39 | 54 | 91 | 49 | 30 | 7 | 3 | 307 |
| %[a] | 12.9 | 14.0 | 10.8 | 10.1 | 6.9 | 7.1 | 5.8 | 3.9 | 2.9 | 7.7 |
| Senility | 3 | 4 | 15 | 15 | 50 | 15 | 16 | 2 | 0 | 120 |
| %[a] | 2.3 | 3.3 | 4.1 | 2.8 | 3.8 | 2.2 | 3.1 | 1.1 | 0.0 | 3.0 |

[a]Percentage of deaths per all causes.

increasing among men and decreasing among women with increasing BMI.

A total of 5,292 (47.1%) and 3,964 (25.5%) deaths occurred prior to 2003 among men and women, respectively. Those who had moved out of the study areas numbered 1,208 (4.5%), and they were more likely to be women and older than those who were successfully followed. The average follow-up period was 11.2 years (10.6 years for men, 11.7 years for women). Deaths from malignant neoplasms (ICD10: C00–C97), diseases of the circulatory system (I00–I99), pneumonia (J12–J18), and senility (R54) accounted for 32.6, 32.0, 10.3, and 1.8% of total deaths among men and 26.4, 39.0, 7.7, and 3.0% among women, respectively (Table 2). The proportion of those who died from malignant neoplasms was highest in the normal-range BMI group, but diminished as the BMI fluctuated above or below normal. Mortality from diseases of the circulatory system

**Table 3 Hazard ratios and 95% CI of all-cause mortality according to BMI among men aged 65–79**

| | BMI category | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | <16.0 | 16.0–16.9 | 17.0–18.4 | 18.5–19.9 | 20.0–22.9 | 23.0–24.9 | 25.0–27.4 | 27.5–29.9 | ≥30.0 |
| Total | | | | | | | | | |
| Person-years at risk | 967 | 1,962 | 8,565 | 16,699 | 50,471 | 24,168 | 12,720 | 3,142 | 842 |
| Number of deaths | 94 | 157 | 500 | 831 | 2,149 | 936 | 473 | 115 | 37 |
| Age-adjusted HR | 1.99 | 1.74 | 1.27 | 1.16 | 1.00 | 0.94 | 0.91 | 0.87 | 1.02 |
| Age-adjusted 95% CI | (1.62–2.45) | (1.48–2.05) | (1.16–1.40) | (1.07–1.25) | | (0.87–1.01) | (0.83–1.01) | (0.72–1.05) | (0.74–1.42) |
| Multivariate HR[a] | 1.78 | 1.66 | 1.16 | 1.12 | 1.00 | 0.94 | 0.92 | 0.89 | 0.93 |
| Multivariate 95% CI[a] | (1.45–2.20) | (1.41–1.96) | (1.06–1.28) | (1.04–1.22) | | (0.87–1.02) | (0.83–1.01) | (0.73–1.07) | (0.67–1.29) |
| Not current smokers | | | | | | | | | |
| Person-years at risk | 404 | 1,024 | 3,529 | 7,706 | 26,355 | 14,217 | 7,359 | 2,050 | 552 |
| Number of deaths | 45 | 70 | 203 | 371 | 1,008 | 503 | 260 | 66 | 21 |
| Age-adjusted HR | 2.54 | 1.70 | 1.41 | 1.22 | 1.00 | 0.98 | 1.01 | 0.87 | 1.04 |
| Age-adjusted 95% CI | (1.88–3.43) | (1.33–2.16) | (1.21–1.64) | (1.08–1.37) | | (0.88–1.09) | (0.88–1.16) | (0.67–1.11) | (0.67–1.59) |
| Multivariate HR[a] | 2.24 | 1.72 | 1.29 | 1.20 | 1.00 | 0.98 | 1.01 | 0.82 | 0.87 |
| Multivariate 95% CI[a] | (1.66–3.03) | (1.35–2.20) | (1.11–1.50) | (1.07–1.36) | | (0.88–1.09) | (0.88–1.16) | (0.64–1.05) | (0.56–1.34) |
| Physically active | | | | | | | | | |
| Person-years at risk | 480 | 992 | 4,241 | 8,529 | 25,511 | 11,590 | 5,658 | 1,303 | 385 |
| Number of deaths | 34 | 69 | 201 | 345 | 934 | 399 | 189 | 39 | 11 |
| Age-adjusted HR | 1.57 | 1.84 | 1.22 | 1.08 | 1.00 | 0.98 | 0.95 | 0.83 | 0.69 |
| Age-adjusted 95% CI | (1.12–2.22) | (1.44–2.35) | (1.04–1.42) | (0.95–1.22) | | (0.87–1.10) | (0.81–1.11) | (0.60–1.14) | (0.38–1.25) |
| Multivariate HR[a] | 1.46 | 1.76 | 1.11 | 1.04 | 1.00 | 1.00 | 0.98 | 0.83 | 0.65 |
| Multivariate 95% CI[a] | (1.03–2.06) | (1.37–2.25) | (0.95–1.29) | (0.92–1.18) | | (0.89–1.13) | (0.84–1.15) | (0.60–1.15) | (0.36–1.19) |
| No history of cancer, MI or stroke | | | | | | | | | |
| Person-years at risk | 484 | 1,236 | 5,231 | 10,750 | 33,931 | 15,849 | 8,331 | 2,069 | 548 |
| Number of deaths | 40 | 91 | 282 | 483 | 1,323 | 524 | 289 | 64 | 21 |
| Age-adjusted HR | 1.78 | 1.77 | 1.29 | 1.15 | 1.00 | 0.87 | 0.93 | 0.82 | 1.04 |
| Age-adjusted 95% CI | (1.30–2.44) | (1.43–2.19) | (1.13–1.47) | (1.04–1.28) | | (0.79–0.97) | (0.82–1.06) | (0.63–1.05) | (0.68–1.60) |
| Multivariate HR[a] | 1.68 | 1.80 | 1.20 | 1.14 | 1.00 | 0.91 | 0.93 | 0.84 | 0.99 |
| Multivariate 95% CI[a] | (1.22–2.30) | (1.45–2.23) | (1.05–1.36) | (1.03–1.26) | | (0.82–1.00) | (0.82–1.06) | (0.66–1.09) | (0.64–1.53) |
| Excluded those who died within 3 years | | | | | | | | | |
| Person-years at risk | 920 | 1,209 | 8,407 | 16,472 | 49,949 | 23,952 | 12,612 | 3,104 | 840 |
| Number of deaths | 65 | 124 | 406 | 708 | 1,869 | 818 | 424 | 96 | 36 |
| Age-adjusted HR | 1.72 | 1.68 | 1.21 | 1.15 | 1.00 | 0.94 | 0.93 | 0.83 | 1.15 |
| Age-adjusted 95% CI | (1.34–2.20) | (1.40–2.01) | (1.09–1.35) | (1.05–1.25) | | (0.86–1.02) | (0.84–1.04) | (0.67–1.01) | (0.83–1.60) |
| Multivariate HR[a] | 1.56 | 1.62 | 1.11 | 1.11 | 1.00 | 0.95 | 0.94 | 0.84 | 1.07 |
| Multivariate 95% CI[a] | (1.22–2.00) | (1.35–1.94) | (0.99–1.23) | (1.02–1.21) | | (0.88–1.03) | (0.84–1.04) | (0.69–1.04) | (0.77–1.49) |

CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.
[a]Adjusted for smoking, drinking, physical activity, sleep duration, stress, education, marital status, green vegetables, stroke, MI, cancer (includes unknown groups).

seemed to increase as the BMI increased, except for a minor increase in the severely thin group. Mortality from pneumonia showed an obvious inverse association with BMI, and senility was rare among overweight/obese groups.

Tables 3 and 4 showed the HRs by gender of all-cause mortality by BMI categories. Compared with the mid-normal-range group (BMI: 20.0–22.9), multiple-adjusted HRs of all-cause mortality for underweight groups were statistically higher among both men and women, with the highest mortality risk found in the severely thin group (BMI: <16.0) as 1.78 (95% confidence interval: 1.45–2.20) in men, and 2.55 (2.13–3.05) in women. Even within the normal-range group, the lower normal range (BMI: 18.5–19.9) showed a statistically elevated risk compared with the mid normal range (HR: 1.12 in men and 1.22 in women). In contrast, overweight subjects showed no relation with risk elevation among either men or women.

**Table 4 Hazard ratios and 95% CI of all-cause mortality according to BMI among women aged 65–79**

| | BMI category | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **<16.0** | **16.0–16.9** | **17.0–18.4** | **18.5–19.9** | **20.0–22.9** | **23.0–24.9** | **25.0–27.4** | **27.5–29.9** | **≥30.0** |
| Total | | | | | | | | | |
| Person-years at risk | 2,301 | 3,729 | 11,814 | 20,849 | 65,923 | 37,144 | 26,483 | 9,218 | 3,844 |
| Number of deaths | 132 | 121 | 362 | 536 | 1,322 | 690 | 519 | 179 | 103 |
| Age-adjusted HR | 2.66 | 1.52 | 1.45 | 1.23 | 1.00 | 0.98 | 1.06 | 1.07 | 1.37 |
| Age-adjusted 95% CI | (2.22–3.18) | (1.26–1.83) | (1.29–1.63) | (1.11–1.36) | | (0.90–1.08) | (0.96–1.17) | (0.91–1.25) | (1.12–1.68) |
| Multivariate HR[a] | 2.55 | 1.47 | 1.42 | 1.22 | 1.00 | 0.96 | 1.01 | 0.98 | 1.24 |
| Multivariate 95% CI[a] | (2.13–3.05) | (1.22–1.77) | (1.26–1.59) | (1.11–1.35) | | (0.88–1.06) | (0.92–1.12) | (0.84–1.14) | (1.01–1.52) |
| Not current smokers | | | | | | | | | |
| Person-years at risk | 1,631 | 2,678 | 9,147 | 16,306 | 52,259 | 29,950 | 21,359 | 7,410 | 3,086 |
| Number of deaths | 99 | 88 | 273 | 418 | 1,033 | 544 | 406 | 145 | 75 |
| Age-adjusted HR | 2.89 | 1.53 | 1.43 | 1.23 | 1.00 | 0.98 | 1.06 | 1.09 | 1.24 |
| Age-adjusted 95% CI | (2.35–3.55) | (1.23–1.90) | (1.25–1.63) | (1.10–1.38) | | (0.89–1.09) | (0.94–1.18) | (0.92–1.30) | (0.98–1.57) |
| Multivariate HR[a] | 2.72 | 1.48 | 1.40 | 1.24 | 1.00 | 0.97 | 1.02 | 1.00 | 1.14 |
| Multivariate 95% CI[a] | (2.21–3.35) | (1.19–1.84) | (1.22–1.60) | (1.10–1.39) | | (0.87–1.07) | (0.91–1.14) | (0.84–1.19) | (0.90–1.44) |
| Physically active | | | | | | | | | |
| Person-years at risk | 726 | 1,605 | 5,078 | 9,141 | 29,875 | 16,085 | 11,503 | 3,578 | 1,325 |
| Number of deaths | 32 | 41 | 126 | 200 | 518 | 253 | 171 | 57 | 30 |
| Age-adjusted HR | 2.32 | 1.45 | 1.46 | 1.25 | 1.00 | 1.01 | 1.00 | 1.10 | 1.37 |
| Age-adjusted 95% CI | (1.62–3.31) | (1.05–1.99) | (1.21–1.78) | (1.06–1.47) | | (0.87–1.17) | (0.84–1.19) | (0.84–1.45) | (0.95–1.99) |
| Multivariate HR[a] | 2.17 | 1.41 | 1.42 | 1.23 | 1.00 | 0.99 | 0.97 | 1.02 | 1.37 |
| Multivariate 95% CI[a] | (1.52–3.11) | (1.02–1.94) | (1.17–1.73) | (1.05–1.45) | | (0.85–1.15) | (0.82–1.16) | (0.77–1.34) | (0.95–1.98) |
| No history of cancer, MI or stroke | | | | | | | | | |
| Person-years at risk | 1,477 | 2,327 | 7,659 | 13,739 | 43,948 | 24,071 | 17,939 | 6,164 | 2,233 |
| Number of deaths | 77 | 75 | 225 | 327 | 835 | 439 | 322 | 111 | 53 |
| Age-adjusted HR | 2.53 | 1.57 | 1.49 | 1.22 | 1.00 | 1.03 | 1.05 | 1.09 | 1.32 |
| Age-adjusted 95% CI | (2.01–3.20) | (1.24–1.99) | (1.28–1.72) | (1.07–1.38) | | (0.92–1.15) | (0.93–1.20) | (0.89–1.33) | (1.00–1.74) |
| Multivariate HR[a] | 2.38 | 1.52 | 1.44 | 1.21 | 1.00 | 1.02 | 1.02 | 1.01 | 1.21 |
| Multivariate 95% CI[a] | (1.88–3.01) | (1.20–1.92) | (1.24–1.67) | (1.06–1.37) | | (0.90–1.14) | (0.89–1.16) | (0.83–1.23) | (0.92–1.60) |
| Excluded those who died within 3 years | | | | | | | | | |
| Person-years at risk | 2,269 | 3,697 | 11,722 | 20,709 | 65,577 | 36,995 | 26,351 | 9,164 | 3,825 |
| Number of deaths | 111 | 101 | 319 | 465 | 1,177 | 626 | 464 | 157 | 94 |
| Age-adjusted HR | 2.63 | 1.45 | 1.45 | 1.20 | 1.00 | 1.00 | 1.06 | 1.05 | 1.41 |
| Age-adjusted 95% CI | (2.16–3.19) | (1.18–1.77) | (1.28–1.64) | (1.08–1.34) | | (0.91–1.10) | (0.95–1.18) | (0.89–1.24) | (1.14–1.74) |
| Multivariate HR[a] | 2.52 | 1.40 | 1.42 | 1.20 | 1.00 | 0.98 | 1.02 | 0.97 | 1.28 |
| Multivariate 95% CI[a] | (2.07–3.06) | (1.14–1.72) | (1.25–1.61) | (1.08–1.34) | | (0.89–1.08) | (0.92–1.14) | (0.82–1.15) | (1.04–1.59) |

CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.
[a]Adjusted for smoking, drinking, physical activity, sleep duration, stress, education, marital status, green vegetables, stroke, MI, cancer (includes unknown groups).

In addition, obesity (BMI: ≥30.0) did not elevate the all-cause mortality risk among men, though a slight statistically significant risk was observed among women (HR: 1.24) compared with the mid-normal-range group. Subcohort analyses of noncurrent smokers, physically active subjects, and those without major disease at baseline did not alter the risk estimation dramatically. Excluding events occurring within 3 years also produced no change in the effects on all-cause mortality of the underweight and overweight/obese groups.

## DISCUSSION

Using a dataset of a large population-based cohort study of older Japanese subjects aged 65–79 who were followed for >10 years on average, we found that a BMI between 20.0 and 29.9 was associated with a minimum risk of all-cause mortality. This wide range was unchanged when our analysis was limited to subjects who could be followed for at least 3 years from baseline. Moreover, the results were essentially unchanged when subcohort analyses were conducted of those who were not currently smoking, were physically active, or were without a history of cancer, cardiovascular disease, or stroke.

The key advantages of our study were its large-scale cohort with subjects from all over Japan, a long follow-up period of >10 years, and adjustments for known confounders. These advantages allowed us to adopt narrow categories of BMI to examine the association with all-cause mortality among older adults. Moreover, subcohort analyses could be performed considering several factors which influence both body composition and all-cause mortality, especially among the older adults, such as (i) heavy and lengthy periods of smoking (14,17), (ii) physical activity (11), and (iii) subclinical diseases (12).

Risk elevation among thin older adults with results similar to ours was reported by many other cohort studies (1,18,19). There may be several explanations for this association so commonly observed among older adults. First, because lean mass acts as a nutritional preserve (4), and aging itself results in a decline in immune response, such thin older adults may be less resistant to infection (20). Actually, deaths from pneumonia were more prevalent among underweight subjects compared with normal or overweight subjects in our cohort. Second, preexisting disease may be linked to both thinness and an increased risk of death. As shown in Table 1, there were more older adults among low-BMI subjects compared with those in other groups, suggesting that age-related diseases cause weight loss. However, excluding the first 3 years of follow-up did not alter that result. Though the purpose of this article was to examine the association between BMI and all-cause mortality, further investigations into the effects of BMI on cause-specific mortality may help us to better understand the relationship of BMI to lean and/or fat mass, and susceptibility to death among older adults. Third, a confounding influence of smoking may exist, because smokers tend to lose weight more readily than nonsmokers (21), and smoking is known to reduce life expectancy (22). Even if such a confounding effect should exist, subcohort analysis of noncurrent smokers revealed that thin subjects who did not smoke also had a higher risk of all-cause mortality, which suggests that a confounding effect from smoking is not the main explanation. Nevertheless, we cannot rule out the possibility that, even with a careful determination of known confounding variables in the present analysis, other undetected factors related to increased mortality risk among thin older adults might have confounded the association between BMI and mortality.

Overweight/obesity is related to excess mortality among both younger and middle-aged populations (1,23,24), and the cut-off points recommended by World Health Organization (3) are mainly based on them. Though some studies have found that the risk of death among older adults was associated with obesity/overweight (2,12,18), the meta-analysis by Janssen and Mark showed no risk elevation for overweight subjects (estimated risk 1.00 with 95% confidence interval: 0.97–1.03), and a significant though very small risk elevation for obese subjects (1.10, 1.06–1.13) (4). Our study showed no increased risk elevation in overweight/obese subjects (except in obese (BMI: ≥30.0) women), and our results were not altered even among some subcohorts. Although the reason for these inconsistent findings is unclear, explanations of why the weak or absent effect of overweight/obesity on all-cause mortality was observed among the older adults in our study may include the following. First, some individuals who were susceptible to the adverse effects of a high BMI may have already died in youth or middle-age, whereas the older adults with a high BMI who survived may have developed a resistance to the effect of overweight/obesity (4,25). Because obesity in women was found to be associated with increased mortality, it is also possible that severely obese men might have been underrepresented in the present sample (self-selection). Second, the possible protective effects of being overweight reflected by a high BMI (such as nutritional reserve) may have prevailed over its negative effects on all-cause mortality in the elderly population (4). Third, a recent study has shown that the prevalence of a clustering of cardiometabolic risk factors among normal-weight individuals was higher in older age groups compared with that in young and middle-aged subjects (26). Thus, the elevated risk of mortality in the normal-weight group among older adults may have caused a relative risk reduction in the overweight/obese groups. As a result, the BMI in older adults may not be a reliable predictor of mortality risk, especially that from cardiovascular diseases, because the variability of BMI in this age group does not adequately reflect that of other intermediate variables leading to disease.

There are some study limitations we should discuss. First, our data were based on self-reported rather than measured heights and weights. Spencer *et al.* compared self-reported and measured height, weight, and BMI among subjects aged 35–76 years. They found that height was overestimated and weight was underestimated, resulting in underestimation of BMI, especially among heavier men and women (27). Thus, we could not exclude the possibility that overweight/obese older adults underestimated their BMI more often than those with a normal BMI, and consequently, misclassifications leading to an underestimation of overweight/obese risk may have

occurred. However, according to the same authors (27), normal BMI category men and women were the least likely to be incorrectly allocated to another BMI category, and underweight participants were also less likely to be misclassified into the normal range than overweight/obese subjects, making it somewhat unlikely that overestimations of underweight risk might occur. Second, we have no information on body fat or its distribution, such as the ratio of waist-to-hip circumferences. Both high-body fat and low fat-free mass are known to be independent predictors of overall mortality (28). Moreover, Simpson *et al.* reported that, among women, central adiposity was a better predictor of mortality than BMI (29). A large-scale cohort study among older adults that includes such information will be required to investigate the relationship between body composition and mortality. Finally, it should be kept in mind that we did not examine any relationships between weight history and mortality. Moreover, a review by Bales and Buhr revealed the benefits of maintaining weight in older persons who become obese after age 65 (30). Therefore, the result of our observational study should not be used to dismiss the necessity of weight reduction among all obese older adults. In addition, we do not recommend that underweight older adults should gain weight based on our results, because ours was not an interventional study.

In conclusion, we found an elevated risk of all-cause mortality among thin Japanese older adults and a wide range of BMI between 20.0 and 29.9 that showed the lowest mortality risk to be among both older men and women.

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**DISCLOSURE**

The authors declared no conflict of interest.



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ORIGINAL ARTICLE

# Alcohol Drinking May Not Be a Major Risk Factor for Fatty Liver in Japanese Undergoing a Health Checkup

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**Abstract** The question of whether alcohol drinking is a risk factor for fatty liver as shown by ultrasonography was investigated by both cross-sectional and longitudinal approaches in Japanese undergoing a health checkup. In this cross-sectional study, 32,438 males (49.0 ± 11.9 years old) and 31,009 females (48.2 ± 11.6 years old) receiving a health checkup from 2000 to 2005 were included. Longitudinally, 5,444 males (49.8 ± 10.7 years old) and 4,980 females (50.4 ± 9.3 years old) participating in both 2000 and 2005 were included. Multiple logistic regression analyses were performed for both sexes, adjusted for age, BMI, and smoking. The prevalence of fatty liver in non-, occasional, daily moderate, and daily heavy drinkers was 28.5, 27.5, 18.7, and 19.1% in men and 12.4, 7.7, 5.4, and 6.7% in women, respectively (inverse association, $P \leq 0.05$ for both). Occasional, daily moderate, and daily heavy drinking in men and occasional and daily moderate drinking in women were inversely associated with fatty liver in the cross-sectional study. Daily moderate and heavy drinking appeared protective in men in the longitudinal study. Alcohol drinking may not be a major risk for fatty liver in Japanese undergoing a health checkup.

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**Keywords** Alcohol drinking · Fatty liver · Multiple logistic regression analysis · Health checkup · Screening and diagnosis

**Abbreviations**

| | |
|---|---|
| BMI | Body mass index |
| OR | Odds ratio |
| FBG | Fasting blood glucose |

## Introduction

Fatty liver due to intrahepatic accumulation of lipids is a widely recognized disease, thought to be linked to obesity and alcohol consumption [1–3]. Non-alcoholic fatty liver is recognized as the hepatic consequence of the metabolic syndrome, characterized by abdominal obesity, hypertriglycemia, hyperglycemia, and hypertension [4–6].

It has been controversial whether alcohol drinking causes obesity, although consumption was associated with a greater waist-to-hip ratio, overweight, and fatty liver [7–12]. Alcohol abuse and obesity were found to be equally strong risk factors for fatty liver in the Guangzhou area of China [13]. On the other hand, alcohol drinking may not increase the risk of obesity among US adults, drinking frequency further being inversely associated with the increase in waist circumference and obesity [9–11].

Low to moderate alcohol drinking may lower the risk of type 2 diabetes as well as the metabolic syndrome and cardiovascular mortality [14–19]. Protective effects of low to moderate alcohol drinking on type 2 diabetes may be related to improved insulin sensitivity [20–23]. It is possible that low to moderate alcohol drinking may therefore reduce the fatty liver, which is closely related to insulin resistance [5, 24]. Moderate alcohol drinking may also be a

weaker risk factor for fatty liver than obesity from results for the general population of Northern Italy [25]. Low alcohol drinking, less than 20 g alcohol/day, did not increase the risk for fatty liver in Japanese at a health checkup [26]. Low to moderate alcohol drinking attenuated liver steatosis and non-alcoholic steatohepatitis in severely obese individuals in the USA, possibly by reducing insulin resistance [27]. Moreover, modest wine drinking decreased the prevalence of non-alcoholic fatty liver disease in the Third National Health and Nutrition Survey [28].

Most earlier studies excluded subjects with regular alcohol consumption of more than 20 g/day. Some 54–70% of men and 13% of women in Japan consume more than 23 g alcohol/day [29, 30], drinking behavior being to some extent determined by genetic polymorphisms of alcohol metabolism genes and alcohol-induced liver damage being influenced by the genetic variation of cytochrome P4502EI and alcohol dehydrogenase [31–33]. Therefore, exclusion and selection of categories of drinkers may give rise to misleading results.

In the present cross-sectional and longitudinal investigation, we therefore included all alcohol drinkers in an assessment of risk factors including alcohol drinking for fatty liver assessed by ultrasonography. Adjustment was made for age, body mass index (BMI), and smoking in Japanese undergoing a health checkup.

## Methods

### Design of Study

This study included both cross-sectional and retrospective longitudinal analyses to investigate whether alcohol consumption, determined by questionnaire, is associated with fatty liver, assessed by ultrasonography, in apparently healthy Japanese undergoing a health checkup. Informed consent was obtained from all participants.

### Subjects of the Cross-Sectional Study

A total of 179,646 participants (men: 95,977, 51.7 ± 11.6 years old; women: 83,669, 51.4 ± 11.1 years old) underwent medical examinations including ultrasonography at Okazaki City Medical Association, Public Health Center, between April 2000 and March 2006. Since more than half of the participants repeatedly underwent medical checkups, the participants undergoing a checkup for the first time during this period were included. These comprised 34,593 men and 32,743 women. After exclusion of participants who had past or present histories of hepatic diseases induced by drugs, autoimmune conditions, or unknown etiology based on questionnaire and positive results for hepatitis virus, a total of 63,447 participants (men: 32,438, 49.0 ± 11.9 years old; women: 31,009, 48.2 ± 11.6 years old) were included.

### Subjects of the Longitudinal Study

The numbers of participants undergoing medical checkups including ultrasonograpy in 2000 and 2005 were 26,247 (men: 14,627; women: 11,620) and 32,548 (men: 17,207; women: 15,341), respectively. After exclusion of participants who had past or present histories of hepatic diseases induced by drugs, autoimmune conditions, or unknown etiology based on questionnaire and positive results of hepatitis virus, a total of 12,453 participants in both 2000 and 2005 (men: 6,924, 49.5 ± 10.5 years old; women: 5,529, 50.7 ± 9.3 years old) were included. Since 2,029 cases (men: 1,480, 21.4%; women: 549, 9.9%) were assessed as having fatty liver in 2000 on ultrasonography, a total of 10,424 participants (men: 5,444, 49.8 ± 10.7 years old; women: 4,980, 50.4 ± 9.3 years old) without fatty liver in 2000 were longitudinally analyzed to determine risk factors for newly developed fatty liver on ultrasonography in 2005.

### Questionnaire

Subjects provided data for alcohol consumption and smoking status in a self-administered questionnaire that was then checked during individual interview by expert nurses in the center. Alcohol consumption was recorded using questions on both frequency and quantity. Frequency of drinking was classified into occasional (1–6 days/week) and daily (7 days/week). One drink was defined as one bottle (500 ml) of beer containing 4–5% alcohol or 1 gou (180 ml) of Japanese sake containing 14% alcohol, which is equivalent to 23 g alcohol [29, 30]. Quantities of drinks were recorded as one, two, or three and more than three drinks per day. Amounts of alcohol consumed per week were estimated by assessing both frequency and numbers of drinks only in the daily drinkers since it was difficult to accurately determine amounts of alcohol in the occasional drinkers. The amounts of alcohol in the participants having daily one, two, and three or more than three drinks were estimated to be 161 g/week, 322 g/week, and 483 g or more than 483 g/week, respectively.

The drinkers were divided into three categories: occasional drinkers, daily moderate drinkers who have one drink (23 g alcohol) per day, and daily heavy drinkers who have two and three or more than three drinks (46 g and 69 g or more than 69 g alcohol, respectively) per day. These categories were determined according to the

previous reports demonstrating that less than 30 g alcohol/day prevented cardiovascular diseases and the risk threshold for alcohol-induced liver disease was more than 30 g alcohol/day [34, 35].

### Measurements

Body weight was measured to the nearest 0.1 kg and height to the nearest 0.1 cm. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. BMI was categorized into three categories: <25, 25–29.9, and ≤30 according to the criteria determined by the Japan Society for the Study of Obesity. Age was categorized into four categories: <40, 40–49, 50–59, and <60.

Blood samples were taken from each participant after overnight fasting. Fasting blood glucose (FBG) was measured by Hitachi autoanalyzer models 7600 and 7700 (Hitachi Medical, Co., Tokyo, Japan).

Fasting hyperglycemia was defined if serum FBG was ≤110 mg/dl. Elevated blood pressure or hypertension was diagnosed if resting blood pressures was ≤130/85 mmHg or if the participants had either a history of hypertension or antihypertensive medication, respectively.

Abdominal ultrasonographic examination was performed using convex-type real-time electronic scanners (SSA 250 and 300, Toshiba Medical, Co., Tokyo, Japan) by ten technicians lacking any information about the subjects, including alcohol history. All images were printed on sonograph paper and reviewed by other technicians and physicians. Fatty liver was assessed according to the modified criteria reported previously [36, 37]. These include a comparative assessment of liver brightness (diagnosed by a difference of more than 10 in the average liver and renal cortical echo amplitudes), attenuation of echo penetration, and decreased visualization of veins.

### Statistical Analyses

Multiple logistic regression analyses were performed to determine the influence of drinking as a risk factor for fatty liver in both men and women, both adjusted for age and for age, BMI, and smoking in the cross-sectional and longitudinal studies. Adjustment was also made for age, BMI, smoking, and either FBG or elevated blood pressure and hypertension. The analyses were further performed after excluding daily heavy drinkers.

Statistical differences among groups were identified using one-way analysis of variance, followed by multiple comparisons using Bonferroni method. The $m \times n$ chi-square test and Fisher's test were used for comparison of prevalence of fatty liver. Logistic regression analyses were performed using computer software (SPSS version 13.0 for Windows). $P$ values less than 0.05 were considered significant.

## Results

### Cross-Sectional Study

The percentages of occasional, daily moderate, and daily heavy drinkers were 32.9, 17.7, and 9.3% overall, 33.8, 27.6, and 16.5% for men, and 32.1, 7.4 and 1.8% for women, respectively. Age was significantly lower in occasional and daily drinkers than in non-drinkers in both sexes (Table 1). BMI was significantly higher in occasional drinkers and lower in daily drinkers than in non-drinkers in men and was significantly lower in occasional and daily drinkers than in non-drinkers in women. In addition, the overall prevalence of fatty liver was 23.9% in men and 10.3% in women, and the prevalence of fatty liver in daily

**Table 1** Age, BMI, prevalence of fatty liver, and ever smoking rates due to drinking habits in the cross-sectional study

| | Non-drinkers | Occasional drinkers | Daily moderate drinkers | Daily heavy drinkers |
|---|---|---|---|---|
| *Men* | | | | |
| % | 21.7 | 33.8 | 27.6 | 16.5 |
| Age | 50.9 ± 12.6 | 46.4 ± 12.1* | 50.7 ± 11.2 | 49.1 ± 10.7* |
| BMI | 23.1 ± 3.2 | 23.4 ± 3.1* | 22.9 ± 2.8 | 23.0 ± 2.8 |
| Fatty liver (%) | 28.5 | 27.5 | 18.7 | 19.1 |
| Ever smoking rates (%) | 41.1 | 41.3 | 44.4 | 59.6 |
| *Women* | | | | |
| Number (%) | 58.5 | 32.1 | 7.4 | 1.8 |
| Age | 50.6 ± 11.4 | 44.3 ± 11.2* | 47.5 ± 10.0* | 42.7 ± 10.1* |
| BMI | 22.2 ± 3.3 | 21.7 ± 3.1* | 21.4 ± 2.8* | 21.2 ± 3.0* |
| Fatty liver (%) | 12.4 | 7.7 | 5.4 | 6.7 |
| Ever smoking rates (%) | 5.9 | 11.6 | 17.3 | 52.4 |

* $P < 0.05$ compared with non-drinkers

drinkers was significantly lower than in non-drinkers in both sexes.

Multiple logistic regression analysis revealed that occasional and daily moderate drinking both adjusted for age and for age, BMI, and smoking was inversely associated with fatty liver in both sexes (Table 2). Daily heavy drinking fully adjusted for other factors was inversely associated with fatty liver in men, while this relation did not reach statistical significance in women.

Adding FBG or elevated blood pressure and hypertension, the ORs were not changed in both sexes. After removing the daily heavy drinkers (5,370 men and 563 women), the results were not essentially changed (data not shown).

## Longitudinal Study

The percentages of occasional, daily moderate, and daily heavy drinkers were 30.6, 20.3, and 9.5% overall, 31.3, 32.3, and 17.0% for men, and 29.9, 7.0, and 1.2% for women, respectively. Age was significantly lower in occasional and daily heavy drinkers in men and in three groups of drinkers in women than in non-drinkers (Table 3). Fatty liver newly developed in 10.2, 12.1, 11.7, and 12.0% of non-, occasional, daily moderate, and daily heavy drinkers, respectively, overall within the 5-year period. Fatty liver was found in 16.4, 16.7, 12.9, and 12.4% of non-, occasional, daily moderate, and daily heavy drinkers in men, respectively, and in 8.2, 6.8, 5.7, and 6.7% of the women, respectively. The risk of newly developed fatty liver was significantly lower in daily moderate and heavy drinkers than non-drinkers in men.

In the multiple logistic regression analysis, daily moderate and heavy drinking was inversely associated with fatty liver adjusted for age, BMI, and smoking in men. Although similar inverse association was observed in women, this did not reach statistical significance (Table 4). Adding FBG or elevated blood pressure and hypertension did not alter the ORs (data not shown). After removing the daily heavy drinkers (928 men and 60 women), daily moderate drinking was the inverse risk factor for fatty liver (ORs 0.72, 95% CI 0.58–0.89) in men, while the results were not changed in women.

**Table 2** Multiple logistic regression analysis for fatty liver in the cross-sectional study

| | Age-adjusted OR | 95% CI | Multivariate OR* | 95% CI |
|---|---|---|---|---|
| *Men* | | | | |
| Non-drinkers | 1.00 | References | 1.00 | References |
| Occasional drinkers | 0.93 | 0.87–0.99 | 0.89 | 0.83–0.96 |
| Daily moderate drinkers | 0.56 | 0.52–0.60 | 0.58 | 0.53–0.63 |
| Daily heavy drinkers | 0.56 | 0.51–0.61 | 0.57 | 0.52–0.63 |
| *Women* | | | | |
| Non-drinkers | 1.00 | References | 1.00 | References |
| Occasional drinkers | 0.74 | 0.68–0.81 | 0.77 | 0.70–0.85 |
| Daily moderate drinkers | 0.44 | 0.37–0.53 | 0.53 | 0.43–0.64 |
| Daily heavy drinkers | 0.70 | 0.50–0.98 | 0.85 | 0.60–1.23 |

* Adjusted by age, BMI, and smoking status

**Table 3** Age, BMI, and ever smoking rates due to drinking habits in the longitudinal study

| | Non-drinkers | Occasional drinkers | Daily moderate drinkers | Daily heavy drinkers |
|---|---|---|---|---|
| *Men* | | | | |
| Number (%) | 19.1 | 31.3 | 32.3 | 17.0 |
| Age | 51.4 ± 11.2 | 48.7 ± 11.1* | 50.3 ± 10.5 | 49.0 ± 9.5* |
| BMI | 22.2 ± 2.6 | 22.5 ± 2.5* | 22.4 ± 2.4 | 22.4 ± 2.4 |
| Ever smoking rates (%) | 39.0 | 41.8 | 44.6 | 63.9 |
| *Women* | | | | |
| Number (%) | 61.5 | 29.9 | 7.0 | 1.2 |
| Age | 51.8 ± 9.2 | 47.9 ± 9.2* | 49.6 ± 8.6* | 46.8 ± 9.0* |
| BMI | 21.8 ± 2.6 | 21.8 ± 2.6 | 21.5 ± 2.5 | 21.5 ± 2.7 |
| Ever smoking rates (%) | 4.3 | 9.2 | 17.7 | 53.5 |

* $P < 0.05$ compared with non-drinkers

**Table 4** Multiple logistic regression analysis for fatty liver in the longitudinal study

| | Age-adjusted OR | 95% CI | Multivariate OR* | 95% CI |
|---|---|---|---|---|
| *Men* | | | | |
| Non-drinkers | 1.00 | References | 1.00 | References |
| Occasional drinkers | 0.97 | 0.78–1.19 | 0.95 | 0.77–1.17 |
| Daily moderate drinkers | 0.73 | 0.59–0.90 | 0.72 | 0.58–0.89 |
| Daily heavy drinkers | 0.67 | 0.52–0.87 | 0.65 | 0.50–0.85 |
| *Women* | | | | |
| Non-drinkers | 1.00 | References | 1.00 | References |
| Occasional drinkers | 0.83 | 0.65–1.05 | 0.81 | 0.63–1.04 |
| Daily moderate drinkers | 0.67 | 0.42–1.07 | 0.71 | 0.44–1.16 |
| Daily heavy drinkers | 0.08 | 0.29–2.26 | 0.74 | 0.25–2.17 |

* Adjusted by age, BMI, and smoking status

## Discussion

The present study demonstrated that alcohol drinking may not be a major risk factor for fatty liver as assessed by ultrasonography in Japanese undergoing a health checkup. Thus, the prevalence of fatty liver in both sexes was significantly lower in daily drinkers than in non-drinkers. Occasional, daily moderate, and daily heavy drinking in men and occasional and daily moderate drinking in women fully adjusted for other factors were inversely associated with fatty liver in the cross-sectional study. Daily moderate and heavy drinking exerted protective effects against the development of fatty liver in men in the longitudinal study.

The low to moderate amounts of alcohol found to reduce type 2 diabetes, metabolic syndrome, and cardiovascular diseases have ranged widely [14–23]. However, low to moderate amounts of alcohol were usually defined as less than 30 g alcohol/day [34, 35, 38]. Further, the risk for cardiovascular diseases is lower when alcohol consumption is low to moderate, and the risk is higher when alcohol consumption is high, resulting in a dose-response curve that is J- or U-shaped [38]. It was also demonstrated that the threshold for non-cirrhotic and cirrhotic liver damage was reported to be less than 30 g alcohol/day, and risk increased with increasing daily intake [35, 39]. We estimated that alcohol consumption of daily heavy drinkers ranged from 46 g alcohol/day to 69 g or more than 69 g alcohol/day in the present study. We also demonstrated that even daily heavy drinking was inversely associated with fatty liver and that exclusion of daily heavy drinkers did not essentially alter the trend in both cross-sectional and longitudinal studies. However, we do not encourage heavy alcohol drinking since we focused the effect on fatty liver, but not on liver injury, and more than 30 g alcohol/day has been reported to be injurious to the liver [35, 39].

Ethanol is known to impair fat oxidation and stimulate lipogenesis in the liver [2, 3]. Although there is conflicting evidence, alcohol intake is reported to be associated with fatty liver in apparently healthy adult men in Spain, with alcohol abuse and obesity being equally strong risk factors for fatty liver in the Guangzhou area of China [12, 13]. Alcohol drinking was found to be a weaker risk factor for fatty liver than obesity in another study [25].

Although our results appear paradoxical on the surface, we speculate that the discrepancy may be related to the different proportion of heavy alcohol drinkers. Our results are in line with other reports that low alcohol drinking did not increase the risk for fatty liver in health checkup participants in Japan and that low to moderate alcohol drinking reduced liver steatosis and non-alcoholic steatohepatitis found in the severely obese in the USA [26, 27]. Further, it was recently demonstrated that modest wine consumption was associated with a reduced prevalence of non-alcoholic fatty liver disease [28].

Adding FBG or elevated blood pressure and hypertension did not alter the ORs in both cross-sectional and longitudinal studies, suggesting that the relationship between alcohol drinking and fatty liver was not confounded by these factors and the effect of alcohol drinking on fatty liver may be independent of improved glucose metabolism and endothelial function. The mechanism by which low to moderate alcohol drinking reduces type 2 diabetes, cardiac ischemic diseases, and the metabolic syndrome may be, in part, related to increased insulin sensitivity [20–23]. Insulin resistance causes accumulation of fat in the hepatocytes through lipolysis and hyperinsulinemia [4, 40]. Although we did not measure insulin sensitivity in the present study, we speculate that this may be increased in our population by alcohol drinking, thereby attenuating fatty liver.

A major limitation of the present study was the cross-sectional and retrospective longitudinal design. The subjects were limited to the Japanese participants undergoing a health checkup. Although it would have been preferable to follow up all participants in 2000 to investigate the risk factor for fatty liver in 2005 in a cohort manner, only 42.5% of the participants in 2000 received the medical checkup in 2005. In addition, alcohol consumption was

self-reported, and the drinkers were roughly divided into four groups according to the frequency of drinking for logistic regression analyses, which may result in inaccuracies. Finally, although histological diagnosis is more accurate, we had to rely on ultrasonography for the purposes of the present study. Ultrasonography cannot distinguish steatosis and steatohepatitis, with the result that it may be unclear if the participants drinking alcohol have liver damage. However, it has been widely used to assess fatty liver since it is a non-invasive procedure with relatively high sensitivity and specificity for screening purposes [1, 12, 13, 25, 26, 36, 37]. The prevalence of fatty liver, 23.9% in men and 10.3% in women in the present study, is consistent with values in a previous Japanese report [41].

In conclusion, alcohol drinking may not be a major risk factor for fatty liver on ultrasonography in Japanese undergoing a health checkup. However, we should be prudent, and the available data do not yet provide a rationale for encouragement of alcohol consumption. Future cohort studies assessing the influence of differing amounts of alcohol are necessary to confirm whether alcohol drinking may indeed not be a risk for fatty liver.

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# Antiphosphatidylethanolamine antibodies might not be an independent risk factor for further miscarriage in patients suffering recurrent pregnancy loss

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ABSTRACT

The prevalence of antiphosphatidylethanolamine antibodies (aPEs) is higher in recurrent pregnancy loss patients than that in women with normal pregnancy. We conducted a cohort study to examine the predictive value of aPE for recurrent pregnancy loss and to determine its clinical significance. We examined plasma protein dependent (P+) and independent (P−) aPE IgG and IgM antibodies in 367 women with two or more unexplained consecutive pregnancy losses. We also examined conventional antiphospholipid antibodies (aPL) such as β2-glycoprotein I-dependent anticardiolipin antibodies (β2GPI-dependent aCL), lupus anticoagulant with reference to the dilute activated partial thromboplastin time (aPTT) and the diluted Russell's viper venom time (RVVT). Subsequent pregnancy outcome without medication was examined, and patients with and without aPE were compared. Totals of 37 (10.1%), 14 (3.8%), 23 (6.3%), 6 (1.6%), 9 (2.5%), 10 (2.7%) and 50 (13.6%) of the 367 patients were, respectively, positive for P+aPE IgG, P− aPE IgG, P+aPE IgM, P− aPE IgM, β2GPI-dependent aCL, lupus anticoagulant by RVVT and LA by aPTT. The patients with aPE differed from patients with β2GPI-dependent aCL or lupus anticoagulant by RVVT. No difference in live birth rate was apparent between positive and negative aPE patients with no medication. The areas under the curves for each ROC curve for the four aPEs were 0.535, 0.612, 0.546 and 0.533, respectively, so there was no significant variation in diagnostic capacity. We did not obtain any evidence that aPE elevation is an independent risk factor to predict further miscarriage in recurrent pregnancy loss patients.



## 1. Introduction

Established causes of recurrent pregnancy loss are abnormal chromosomes in either partner, particularly translocations, antiphospholipid antibodies (aPL) and uterine anomalies (Farquharson et al., 1984; Sugiura-Ogasawara et al., 2004, 2010). The antiphospholipid syndrome (APS) is the most important treatable etiology (Rai et al., 1997). The Sapporo criteria have been used to define APS since 1999 and preliminary classification criteria were revised more recently at a workshop in Sydney (Miyakis et al., 2006). With the new international criteria, patients can be diagnosed with APS when lupus anticoagulant and/or anticardiolipin antibodies (aCL) continue to be elevated for 12 weeks. Patients with persistent aPL should be treated with low dose aspirin and heparin combined therapy during pregnancy and about 70–80% can then experience a live birth (Rai et al., 1997).

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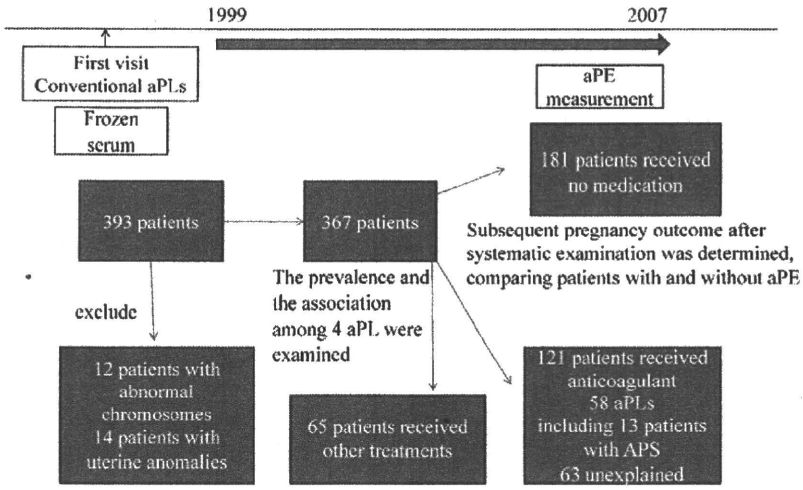


**Fig. 1. Study profile.**

Many kinds of aPL including antibodies against cardiolipin (CL), phosphatidylserine, phosphatidylinositol, phosphatidylethanolamine (PE), have been measured by ELISA methods. β2-glycoprotein I (β2GPI) was found to be the true antigen of aCL in 1990 (Matsuura et al., 1990). Recently, aPL have been recognized to be autoantibodies to phospholipid-binding plasma proteins. The most common antigens are β2GPI and prothrombin (Roubey et al., 1992). β2GPI-dependent aCL, anti-β2GPI antibodies and lupus anticoagulant detected by the methods described in the International Thrombosis and Homeostasis Society are included in the International criteria for APS (Miyakis et al., 2006).

Sugi and McIntyre (1995) reported that certain antiphosphatidylethanolamine antibodies (aPEs) are not specific for PE per se but are directed to PE-binding plasma proteins, such as high molecular weight kininogen, low molecular weight kininogen, and proteins in complexes with kininogen, factor XI, or prekallikrein. The prevalence of aPE IgG and IgM were reported to be 20.1 and 12.2%, respectively, in patients suffering early pregnancy losses and significantly higher than in controls (Sugi et al., 1999). In contrast, rates for β2GPI-dependent aCL and lupus anticoagulant by dilute Russell's viper venom time (RVVT) were only 0.7 and 1.4%, respectively (Sugi et al., 1999).

However, to our knowledge, there are only limited data for any association between aPE and adverse pregnancy outcome in recurrent pregnancy loss cases (Gris et al., 2000). Thus, aPEs are not included in the international criteria for APS. We therefore here examined the predictive value of aPE and associations among β2GPI-dependent aCL and lupus anticoagulant for recurrent pregnancy loss to determine the clinical significance of aPE.

## 2. Materials and methods

### 2.1. Patients

Hysterosalpingography, chromosome analysis for both partners, determination of conventional aPLs, including both lupus anticoagulant by the 5 times diluted activated partial thromboplastin time (aPTT) method and the diluted RVVT method and β2GPI-dependent aCL, and blood tests for hyperthyroidism, diabetes mellitus and hyperprolactinemia were performed for all patients at the first visit of Nagoya City University Hospital. Serum for aPE measurement was taken at the same time when conventional aPL were measured and frozen at −70 °C. In total, we studied 367 women who had a history of two or more consecutive pregnancy losses. None of the patients had any readily identifiable causes of recurrent pregnancy loss, such as uterine or chromosomal abnormalities in either partner. None had received any medication before examination and there was no history of thrombosis. Their mean age was 31.9 ± 4.3 and the average number of previous early pregnancy losses was 2.7 ± 1.1. Twenty-two patients had a history of 26 events of intrauterine fetal death.

The patients' plasma protein dependent (P+) and independent (P−) aPE IgG and IgM were measured as aPE in 2007 using stored serum. aPE was measured once. The 367 pregnancies were recorded from August 1999 to December 2007 and subsequent pregnancy outcome was examined prospectively. A total of 58 patients were positive for at least one kind of conventional aPLs and 13 were diagnosed as APS, according to the Sapporo criteria and the Sydney revision. Sixty-three patients with unexplained causes were also treated with low dose aspirin and heparin therapy. Some 181 patients received no medication. Some 65 patients who received luteal support and a biological response modifier were excluded (Katano et al., 2000). The study profile is shown in Fig. 1.

Gestational age was calculated from basal body temperature charts. Ultrasonography was performed once or twice a week from 4 to 8 weeks' gestation. Dilation and curettage were carried out when miscarriages were diagnosed, and the karyotypes of aborted conceptuses were determined with the use of a standard G-banding technique. The present study was approved by the Research