Original Contribution

Branched-chain Amino Acid Intake and the Risk of Diabetes in a Japanese Community

The Takayama Study

Chisato Nagata*, Kozue Nakamura, Keiko Wada, Michiko Tsuji, Yuya Tamai, and Toshiaki Kawachi

* Correspondence to Dr. Chisato Nagata, Department of Epidemiology and Preventive Medicine, Graduate School of Medicine, Gifu University, 1-1 Yanagido, Gifu City 501-1194, Japan (e-mail: chisato@gifu-u.ac.jp).

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Dietary supplementation with branched-chain amino acids (BCAAs), including leucine, isoleucine, and valine, has shown potential benefits for the metabolic profile. However, higher blood BCAA levels have been associated with insulin resistance. To our knowledge, there has been no study on dietary BCAAs and the risk of diabetes. We examined the association between BCAA intake and risk of diabetes in a population-based cohort study in Japan. A total of 13,525 residents of Takayama City, Japan, who enrolled in a cohort study in 1992 responded to a follow-up questionnaire seeking information about diabetes in 2002. Diet at baseline was assessed by means of a validated food frequency questionnaire. A high intake of BCAAs in terms of percentage of total protein was significantly associated with a decreased risk of diabetes in women after controlling for covariates; the hazard ratio for the highest tertile versus the lowest was 0.57 (95% confidence interval: 0.36, 0.90; P-trend = 0.02). In men, leucine intake was significantly marginally associated with the risk of diabetes; the hazard ratio for the highest tertile versus the lowest was 0.70 (95% confidence interval: 0.48, 1.02; P-trend = 0.06). Data suggest that a high intake of BCAAs may be associated with a decrease in the risk of diabetes.

amino acids; branched-chain amino acids; cohort studies; diabetes; diet

Abbreviations: BCAA, branched-chain amino acid; CI, confidence interval; FFQ, food frequency questionnaire; MET, metabolic equivalent.

The branched-chain amino acids (BCAAs) leucine, isoleucine, and valine are essential amino acids. BCAAs can be oxidized in skeletal muscle, whereas other essential amino acids are catabolized mainly in the liver (1). Skeletal muscle is the main target of glucose use and insulin activity, which causes protein anabolism (2). Glucose is taken from nutrients by the muscles and stored by insulin activity as glycogen. Degradation of the BCAAs in skeletal muscle has been linked to the maintenance of glucose homeostasis, because BCAAs may improve muscle glucose uptake by enhancing recycling of glucose via the glucose-alanine cycle and may regulate muscle protein synthesis translationally through the insulin signaling cascade (3, 4). The beneficial effects of BCAA supplementation on metabolic control have been reported in patients with type 2 diabetes and chronic liver disease (5–7). However, on the other hand, higher plasma BCAA levels have been associated with insulin resistance or diabetes (8–13).

To our knowledge, there has been no report on the association between dietary BCAAs and the risk of diabetes in normal subjects. We examined this association in a population-based cohort study of Japanese men and women, the Takayama Study (14).

MATERIALS AND METHODS

The Takayama Study

Subjects in this study were cohort members from a population-based cohort study conducted in Takayama City, Gifu Prefecture,
Japan. The Takayama Study was initiated in 1992 to identify dietary and lifestyle factors in relation to morbidity from chronic diseases. A total of 31,552 Takayama residents aged 35 years or more completed a self-administered baseline questionnaire which included questions on demographic characteristics, smoking, diet, physical activity, and medical and reproductive histories, yielding a participation rate of 85.3%. The rationale and design of the Takayama Study are described in detail elsewhere (14).

Diet, including alcohol intake, was assessed with a validated 169-item semiquantitative food frequency questionnaire (FFQ). The questionnaire asked participants how often on average they had consumed each of the food items or dishes listed during the year prior to the study and what the usual serving size of each item was. A total of 511 foods were covered by the FFQ. Nutrient intake was computed by multiplying the frequency of consumption of each food by the nutrient content of the specified portion. Values for amino acids and other nutrients were obtained from the "Standard Tables of Food Composition in Japan, Fifth Revised and Enlarged Edition (15). Because amino acid data are not available for 117 (22.9%) foods in the Japanese standard tables of food composition, values published by the US Department of Agriculture (http://www.ars.usda.gov/Main/site_main.htm?modecode=12-35-45-00) were also used for estimation of amino acid intake. Fatty acid composition was evaluated using data published by Sasaki et al. (16). A detailed description of the FFQ, its reliability and validity, and the method used for calculating nutrient intakes has been published previously (17, 18). The FFQ was validated in this population by comparing 3-day diet records, four 24-hour recalls, and 12 daily diet records kept over a 1 year period (17). For example, the Spearman correlation coefficients for correlation between the questionnaire and 12 daily diet records kept over a 1-year period for major nutrients and micronutrients ranged from 0.20 for cholesterol to 0.78 for calcium in men and from 0.29 for carotene to 0.73 for calcium in women. We additionally evaluated the validity of amino-acid intake estimation. The corresponding Spearman correlation coefficients for intakes of leucine, isoleucine, valine, and total protein were 0.48, 0.60, 0.56, and 0.38, respectively, in men and 0.71, 0.56, 0.63, and 0.63, respectively, in women.

Physical activity was assessed by asking participants to report the average number of hours per week they had spent performing various kinds of activities during the past year. The amount of time per week spent at each intensity of activity was multiplied by its corresponding energy expenditure requirements, expressed in metabolic equivalents (METs), and summed to yield a physical activity score (MET-hours/week). Details on the physical activity measure, including its validity, are given elsewhere (19, 20).

Follow-up and endpoints

Subjects for the present follow-up study were restricted to those who were less than 70 years of age at baseline (n = 26,546). In July 2002, a follow-up questionnaire seeking information about diabetes was sent to these persons. Deaths and moves in this cohort were certified by means of the residential registry. After exclusion of persons who were deceased (n = 1,505), were physically unable to complete the questionnaire (n = 51), or had moved (n = 2,598), the study population consisted of 22,392 persons, of whom 14,975 (66.9%) responded to the follow-up questionnaire. Compared with nonrespondents to the follow-up questionnaire, respondents were more likely to be older, better educated (≥15 years), and never smokers and had lower intakes of alcohol and coffee, as described elsewhere (21, 22). BCAA intakes in terms of percentage of total protein intake were similar between respondents and nonrespondents (17.23% and 17.18%, respectively, in men and 17.32% and 17.29%, respectively, in women), and the difference was not significant after controlling for age. The specific endpoint of this study was the onset of diabetes. The participants who developed diabetes between baseline and follow-up were identified by means of the questionnaire. Participants were asked whether diabetes had been diagnosed by a physician and, if so, at what age. The validity of self-reported diabetes was assessed in a subgroup of participants who provided a blood sample (n = 214). The sensitivity and specificity of self-reported diabetes as compared with the reference standard, defined by hemoglobin A1c level (≥6.1%), were 57.4% and 96.5%, respectively. For the present analysis, we excluded subjects who reported having or having had cancer (n = 274), diabetes (n = 541), or stroke or coronary heart disease (n = 535) at baseline. We further excluded participants who were newly identified as having diabetes at baseline from the follow-up questionnaire (n = 100). In total, 13,525 subjects (5,885 men and 7,640 women) were included in our analyses. Informed consent was obtained from each subject. This study was approved by the institutional review board of the Gifu University Graduate School of Medicine.

Statistical analysis

Total BCAA intake (sum of leucine, isoleucine, and valine intakes) and total protein intake were highly correlated. Therefore, total BCAA intake was expressed as a percentage of total protein intake based on the report by Qin et al. (23). Subjects were divided into 3 equal groups according to tertile of total BCAA intake. Since 30 men and 10 women who developed diabetes during the follow-up period did not provide information regarding the time of diagnosis, we assigned median values for time to diagnosis among persons who developed diabetes for men and women separately. Using a Cox proportional hazards model, we calculated the hazard ratios for incident diabetes in each category (and their 95% confidence intervals) in comparison with the lowest intake category. The median total BCAA value in each category was used to assess linear trend. First, we included only age in the models as a covariate. Additional adjustment was made for non-dietary factors, including level of education (≤11, 12–14, or ≥15 years, or missing data), body mass index (weight (kg)/height (m)²; <21, 21–22.9, 23–24.9, 25–26.9, ≥27, or missing data), physical activity (MET-hours/week), smoking status (men: never smoker, former smoker, current smoker with ≤30 years of smoking, current smoker with >30 years of smoking, or missing data; women: never smoker, former smoker, current smoker, or missing data), history of hypertension (yes or no), and menopausal status (yes or no); women
only), and dietary factors, including glycemic load and daily intakes (continuous) of saturated fat, dietary fiber, alcohol, and coffee. (Glycemic load is defined as the amount of each carbohydrate consumed multiplied by its respective glycemic index. The glycemic index ranks carbohydrate foods on the basis of their postprandial blood glucose response (24.).) The associations of individual BCAAs with the risk of diabetes were evaluated in a similar way. All of the statistical analyses were performed using SAS programs (SAS Institute Inc., Cary, North Carolina). Significance was defined as a 2-sided P value less than 0.05.

RESULTS

Characteristics of the study population, by sex and tertile of total BCAA intake (percentage of total protein intake), are shown in Table 1. Men and women who had a greater intake of total BCAAs were more likely to be older and less educated (<15 years) and to have reported a history of hypertension. They also had lower intakes of dietary fiber, alcohol, and coffee and higher intakes of saturated fat and total protein. In addition, women who had a greater intake of total BCAAs were more likely to be postmenopausal and never smokers. Men who had a greater intake of total BCAAs had a higher dietary glycemic load. Major food groups supplying BCAAs were cereals/potatoes and starches, fish and shellfish, and meats. The contributions (as a percentage of total amount of BCAAs) of these food groups to BCAA intake were 24.6%, 23.2%, and 14.9%, respectively, in men and 22.7%, 20.7%, and 13.7%, respectively, in women. Our questionnaire was designed to measure an individual’s relative intake of nutrients rather than absolute values. Although we present the mean values for nutrients in Table 1, some of them may have been overestimated by our questionnaire. The mean values estimated from the FFQ were generally higher than those estimated from 12 daily diet records; for example, the mean estimate of total protein in the former was 8% higher in men and 14% higher in women than in the latter.

During a 10-year follow-up period, 438 participants reported the development of diabetes. The hazard ratios and 95% confidence intervals for diabetes according to tertiles of total BCAAs and constituent amino acids are shown in Table 2. In men, total BCAA intake was not significantly associated with the risk of diabetes after controlling for covariates. However, compared with the lowest intake, the highest tertile of leucine intake was marginally significantly associated with a decrease in the risk of diabetes (P = 0.06). The trend toward greater reduction in the risk of diabetes with increasing leucine intake was also of borderline significance (P = 0.06). In women, a high intake of total BCAAs was significantly inversely associated with the risk of diabetes, and the trend was also significant. A similar association was observed for each individual BCAA, although the association was somewhat weaker and nonsignificant for isoleucine.

Analysis stratified according to body mass index (<25 or ≥25) showed that this variable did not greatly affect the associations between BCAA intake and diabetes. For example, in men, the hazard ratios for the highest tertile of leucine versus the lowest were 0.73 (95% confidence interval (CI): 0.45, 1.18; P-trend = 0.19) and 0.58 (95% CI: 0.31, 1.09; P-trend = 0.09), respectively, for these 2 body mass index groups. The corresponding values for total BCAAs in women were 0.53 (95% CI: 0.30, 0.96; P-trend = 0.04) and 0.75 (95% CI: 0.35, 1.62; P-trend = 0.45). Exclusion of persons with diabetes that developed during the first 3 years did not alter the results substantially; for example, the hazard ratios for the highest tertile of intake versus the lowest were 0.70 (95% CI: 0.40, 1.08; P-trend = 0.10) for leucine in men and 0.55 (95% CI: 0.34, 0.90; P-trend = 0.02) for total BCAAs in women.

DISCUSSION

In the present prospective study, high intakes of total BCAAs, leucine, and valine were associated with a decreased risk of diabetes in women. In men, leucine intake was marginally significantly inversely associated with the risk of diabetes. Our results suggest a beneficial effect of dietary leucine or BCAAs in preventing diabetes. However, at present, conflicting data exist on the role of BCAAs as a mechanism for the observed association. Leucine or BCAA supplementation has exerted beneficial effects on the metabolic profiles of obese subjects and patients with diabetes or chronic liver disease (5–7), which supports our findings. However, findings from studies based on plasma BCAA levels have suggested rather that BCAAs may promote insulin resistance (8–13, 25). Plasma BCAA levels were higher in obese subjects than in lean subjects and were positively correlated with insulin resistance (25). A recent nested case-control study in the Framingham Offspring Study (10) showed that plasma BCAA levels were correlated with fasting insulin levels and could predict future risk of diabetes, especially in obese persons and those with elevated fasting glucose levels. Plasma BCAA level was associated with insulin resistance in young normoglycemic adults at baseline and 6-year follow-up (11) and in obese subjects after weight loss (12). However, in general, observed blood amino acid patterns are probably not a direct reflection of diet-derived amino acids. McCormack et al. (13) found that plasma BCAA level, but not dietary BCAA intake, was associated with obesity and insulin resistance measured 18 months later among children and adolescents. Qin et al. (23) reported that a high intake of BCAAs was significantly associated with a lower prevalence of being overweight among apparently healthy middle-aged adults, which contradicts the observations for plasma BCAAs. In fact, we also noted that BCAA intake, either as an absolute measurement or a percentage of protein, was unrelated to plasma BCAA levels (r = 0.004 and r = −0.01, respectively) and insulin resistance (r = 0.04 and r = −0.01, respectively) in another sample of women (n = 850) enrolled in a health check-up program provided by a general hospital in Gifu (unpublished data). The reasons for the elevated plasma BCAA level among obese or insulin-resistant subjects are unknown. However, several studies found that the activity of the BCAA catabolic enzyme was reduced in obese, insulin-resistant rodents (26, 27). In obese humans, blood BCAA levels have been seen to drop significantly and expression of the enzyme branched-chain α-ketohydrogenase has been seen to increase following bariatric surgery (28). Thus, it has been proposed that elevated

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men (n = 5,885)</th>
<th>Women (n = 7,640)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tertile 1 (n = 1,962)</td>
<td>Tertile 2 (n = 1,962)</td>
</tr>
<tr>
<td>Age, years</td>
<td>Mean %</td>
<td>Mean %</td>
</tr>
<tr>
<td></td>
<td>49.8</td>
<td>51.7</td>
</tr>
<tr>
<td>Years of education</td>
<td></td>
<td></td>
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<tr>
<td>≤11</td>
<td>46.2</td>
<td>48.6</td>
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<tr>
<td>12–14</td>
<td>39.1</td>
<td>39.3</td>
</tr>
<tr>
<td>≥15</td>
<td>14.7</td>
<td>12.2</td>
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<td>Never smoker</td>
<td>14.3</td>
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<td>History of hypertension</td>
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<td>17.0</td>
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<td>Postmenopausal (women only)</td>
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<td>Body mass index</td>
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<td>Physical exercise, MET-hours/week</td>
<td>28.1</td>
<td>30.3</td>
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<td>Daily dietary intake</td>
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<tr>
<td>Alcohol, g</td>
<td>57.8</td>
<td>40.1</td>
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<td>Coffee, no. of servings</td>
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<td>0.9</td>
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<tr>
<td>Total energy, kcal</td>
<td>2,702</td>
<td>2,668</td>
</tr>
<tr>
<td>Protein, g</td>
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<td>94.8</td>
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<td>Saturated fat, g</td>
<td>15.3</td>
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<td>Fiber, g</td>
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<td>16.4</td>
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<tr>
<td>Carbohydrate, g</td>
<td>374</td>
<td>376</td>
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<tr>
<td>Glycemic load</td>
<td>223.2</td>
<td>234.9</td>
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</table>

Abbreviation: MET, metabolic equivalent.

a Total branched-chain amino acid intake (sum of leucine, isoleucine, and valine intakes) is expressed as a percentage of total protein intake.
b P values were based on linear regression analysis for continuous variables and on the χ² test for categorical variables.
c Weight (kg)/height (m)².
d Glycemic load was calculated by multiplying the carbohydrate content of each food by its glycemic index (24), multiplying this value by the frequency of consumption, and summing these values for all foods. The measure has no units.
Table 2. Hazard Ratios for the Risk of Diabetes According to Tertile of Branched-chain Amino Acid Intake\textsuperscript{a} Among Men and Women, Takayama Study, Japan, 1992–2002

<table>
<thead>
<tr>
<th>BCAA and Tertile of Intake</th>
<th>Median Intake</th>
<th>No. of Cases</th>
<th>No. of Subjects</th>
<th>HR\textsuperscript{b}</th>
<th>95% CI</th>
<th>HR\textsuperscript{c}</th>
<th>95% CI</th>
<th>P-trend</th>
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<tr>
<td>Total BCAAs</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>1</td>
<td>16.74</td>
<td>106</td>
<td>1,962</td>
<td>1.00</td>
<td>1.00</td>
<td>16.86</td>
<td>64</td>
<td>2,547</td>
</tr>
<tr>
<td>2</td>
<td>17.22</td>
<td>76</td>
<td>1,962</td>
<td>0.71</td>
<td>0.53, 0.96</td>
<td>0.75</td>
<td>0.55, 1.03</td>
<td>17.31</td>
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<td>3</td>
<td>17.69</td>
<td>84</td>
<td>1,961</td>
<td>0.77</td>
<td>0.58, 1.04</td>
<td>0.78</td>
<td>0.54, 1.13</td>
<td>17.76</td>
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<td></td>
<td></td>
<td>0.07</td>
<td></td>
<td>0.17</td>
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<td>Leucine</td>
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<td>2</td>
<td>7.77</td>
<td>82</td>
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<td>0.77</td>
<td>0.58, 1.03</td>
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<td>0.58, 1.09</td>
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<td>3</td>
<td>7.98</td>
<td>78</td>
<td>1,961</td>
<td>0.71</td>
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<td>0.48, 1.02</td>
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<tr>
<td>P-trend</td>
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<td></td>
<td>0.02</td>
<td></td>
<td>0.06</td>
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<tr>
<td>Isoleucine</td>
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<tr>
<td>1</td>
<td>4.17</td>
<td>91</td>
<td>1,962</td>
<td>1.00</td>
<td>1.00</td>
<td>4.21</td>
<td>55</td>
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<tr>
<td>2</td>
<td>4.31</td>
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<td>0.94</td>
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<td>0.94</td>
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<td>3</td>
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<td>2</td>
<td>5.15</td>
<td>74</td>
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<td>0.54, 1.03</td>
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<td>84</td>
<td>1,961</td>
<td>0.76</td>
<td>0.57, 1.01</td>
<td>0.87</td>
<td>0.58, 1.24</td>
<td>5.33</td>
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<td></td>
<td>0.05</td>
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<td>0.42</td>
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</table>

Abbreviations: BCAA, branched-chain amino acid; CI, confidence interval; HR, hazard ratio.
\textsuperscript{a} Total branched-chain amino acid intake (sum of leucine, isoleucine, and valine intakes) is expressed as a percentage of total protein intake.
\textsuperscript{b} Adjusted for age.
\textsuperscript{c} Additionally adjusted for years of education, body mass index, physical activity, smoking status, history of hypertension, glycemic load, menopausal status (women only), and intakes of total energy, total protein, saturated fat, dietary fiber, alcohol, and coffee.
plasma BCAA levels in obese or diabetic subjects are caused, in part, by reduced BCAA catabolism (29). Although stimulation of insulin secretion by BCAA is expected to prevent hyperglycemia, this process might not sufficiently compensate for impaired insulin secretion. In this context, it is possible that BCAAs play different roles in glucose metabolism among persons with insulin-resistant and non-insulin-resistant conditions. We did not include the measurement of blood glucose or insulin level. However, body mass index, which is generally correlated with insulin resistance, did not greatly modify the association between dietary BCAA intake and the risk of diabetes. Although it is not known whether circulating BCAAs are causes/mediators of insulin resistance or by-products of the associated metabolic dysfunction, the present study highlights the need for researchers to consider dietary intake of BCAAs.

Among the individual BCAAs, leucine shows great potency in stimulating the secretion of insulin (30). We observed that leucine, as well as total BCAAs, was significantly inversely associated with the risk of diabetes in women. Although these associations were not significant in men, inverse associations were suggested. Obayashi et al. (31) reported that estradiol increased the activity of the BCAA catabolism enzyme in ovarioectomized rats, suggesting control of BCAA catabolism by estrogen. Hormonal status in women may favor the potentially beneficial effect of dietary BCAAs on the risk of diabetes.

Strengths of our study include the prospective design, validation of the dietary questionnaire, representation of the general population, and information on potential confounders. Several limitations should also be considered. The identification of cases of diabetes was based on self-reports. In a previous study conducted in Japan, relatively high sensitivity and specificity were reported for self-reported diabetes relative to physician-reported diabetes; the sensitivity and specificity were 80.8% and 99.3%, respectively (32). However, no screening for undiagnosed diabetes was done. The sensitivity of self-reported diabetes as compared with the criterion defined by hemoglobin A1c level was low in our subsample, and low sensitivity of self-reported diabetes in comparison with biomarkers has been reported from other studies (33, 34). If subjects who had diabetes but were misclassified as nondiabetic were more likely to have had a high intake of BCAAs than those who were correctly classified as diabetic, the results found in the present study would have been affected. Considering that the rate of response to the follow-up questionnaire was not high, the possibility that subjects who had diabetes participated in the study only when they had a low intake of BCAAs or that those who had no diabetes participated in the study only when they had a high intake of BCAAs should also be considered. However, BCAAs are present in various foods, and their intake was expressed as a percentage of total protein intake. In addition, baseline BCAA intakes were similar between respondents and nonrespondents to the follow-up questionnaire. Therefore, it is not likely that BCAA intake was dependent on the diagnosis of diabetes or participation in the study. Despite the use of a validated FFQ, some degree of misclassification of dietary intake is to be expected, just as in other nutritional epidemiologic studies. However, it is unlikely that incident diabetes cases would be systematically underestimated in our FFQ at baseline. Underlying diseases or preclinical signs at baseline may have affected diet, but it is unlikely that such conditions induced lower consumption of BCAAs without affecting total protein or total energy intake. In addition, exclusion of the first 3 years of follow-up did not substantially change the results. Adjustment for numerous lifestyle and dietary factors did not appreciably affect the results. However, we could not fully establish whether the observed reduction in the risk of diabetes was attributable to other nutrient parameters. We could not obtain information on family history of diabetes.

In conclusion, our findings suggest that dietary leucine or BCAA intake might be associated with the risk of diabetes in adults. Studies focusing on the relationship between dietary intake of BCAAs, especially long-term intake, and diabetes are needed. Because this is, to our knowledge, the first study to have examined the association between BCAA intake and risk of diabetes, replication of these results is required.

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Author affiliations: Department of Epidemiology and Preventive Medicine, Graduate School of Medicine, Gifu University, Gifu, Japan (Chisato Nagata, Kozue Nakamura, Keiko Wada, Michiko Tsuji, Yuya Tamai, and Toshiaki Kawachi).

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