Table 2. Hazard Ratios for the Risk of Diabetes According to Tertile of Branched-chain Amino Acid Intake[a] Among Men and Women, Takayama Study, Japan, 1992–2002

BCAA and Tertile of Intake	Men							Women						
	Median Intake	No. of Cases	No. of Subjects	HR[b]	95% CI	HR[c]	95% CI	Median Intake	No. of Cases	No. of Subjects	HR[b]	95% CI	HR[c]	95% CI
Total BCAAs														
1	16.74	106	1,962	1.00		1.00		16.86	64	2,547	1.00		1.00	
2	17.22	76	1,962	0.71	0.53, 0.96	0.75	0.55, 1.03	17.31	58	2,547	0.87	0.61, 1.24	0.75	0.51, 1.10
3	17.69	84	1,961	0.77	0.58, 1.04	0.78	0.54, 1.13	17.76	50	2,546	0.71	0.49, 1.03	0.57	0.36, 0.90
P-trend					0.07		0.17					0.07		0.02
Leucine														
1	7.56	106	1,962	1.00		1.00		7.60	65	2,547	1.00		1.00	
2	7.77	82	1,962	0.77	0.58, 1.03	0.79	0.58, 1.09	7.80	56	2,547	0.84	0.59, 1.20	0.75	0.51, 1.10
3	7.98	78	1,961	0.71	0.53, 0.96	0.70	0.48, 1.02	7.99	51	2,546	0.72	0.50, 1.04	0.62	0.39, 0.97
P-trend					0.02		0.06					0.08		0.04
Isoleucine														
1	4.17	91	1,962	1.00		1.00		4.21	55	2,547	1.00		1.00	
2	4.31	86	1,962	0.94	0.70, 1.27	0.94	0.68, 1.30	4.33	54	2,547	0.93	0.64, 1.36	0.78	0.51, 1.17
3	4.44	89	1,961	0.98	0.72, 1.31	0.93	0.63, 1.39	4.59	63	2,546	1.05	0.73, 1.51	0.77	0.46, 1.25
P-trend					0.87		0.73					0.78		0.31
Valine														
1	5.00	108	1,962	1.00		1.00		5.03	65	2,547	1.00		1.00	
2	5.15	74	1,962	0.68	0.51, 0.92	0.75	0.54, 1.03	5.18	62	2,547	0.90	0.64, 1.28	0.87	0.58, 1.25
3	5.30	84	1,961	0.76	0.57, 1.01	0.87	0.58, 1.24	5.33	45	2,546	0.62	0.42, 9.91	0.61	0.39, 0.94
P-trend					0.05		0.42					0.01		0.03

Abbreviations: BCAA, branched-chain amino acid; CI, confidence interval; HR, hazard ratio.

[a] Total branched-chain amino acid intake (sum of leucine, isoleucine, and valine intakes) is expressed as a percentage of total protein intake.

[b] Adjusted for age.

[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 ovariectomized 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 A_{1c} 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 higher 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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Ⅴ．資料

厚生労働科学研究　肝炎等克服緊急対策研究事業

「ウイルス性肝疾患患者の食事・運動療法とアウトカム評価に関する研究」

平成25年度第一回総会プログラム

研究代表者　森脇　久隆（岐阜大学大学院医学系研究科消化器病態学）

期　日：平成25年7月23日（火）　14：00-17：00

（13：30より受付開始）

場　所：安保ホール601号室（名古屋市中村区名駅3-15-9）

TEL(052)561-9831

平成25年度　厚生労働科学研究費補助金　肝炎等克服緊急対策事業
「ウイルス性肝疾患患者の食事・運動療法とアウトカム評価に関する研究」
事務局：岐阜大学大学院医学系研究科消化器病態学
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研究代表者 挨拶（研究代表者　森脇久隆）　14：00 ～ 14：05

肝炎等克服緊急対策研究事業の企画及び評価に関する研究班　挨拶

14：05 ～ 14：10

共同研究の経過報告と今後の予定　森脇久隆・白木　亮　14：10 ～ 14：40

「肥満 C 型慢性肝疾患患者における運動療法についての検討」

個別研究の提案　14：40 ～

（途中　休憩 10 分）

1．慢性肝疾患患者におけるサルコペニアの測定と意義

兵庫医科大学内科学　肝・胆・膵科　西口　修平

齋藤　正紀

2．慢性肝疾患患者の栄養状態把握のための簡便な栄養指標の検討

～とくに、筋肉の質と量に注目して～

椙山女学園大学生活科学部管理栄養学科　加藤　昌彦

馬嶋　真子

3．レボカルニチン製剤投与中のＣ型肝硬変患者に対する運動療法の有用性の検討（アウトカム評価）

愛知医科大学大学院医学研究科医学教育センター　福澤　嘉孝

4．「肝硬変患者における体力測定と運動指導の効果」「サルコペニアと肝癌との関連」

佐賀大学医学部内科学　肝臓・糖尿病・内分泌内科　水田　敏彦

井手　康史

5．肝癌肝切除における ESSENSE（術後早期回復プログラム）による周術期管理の実践について

関西医科大学外科　海堀　昌樹

6．肥満・高血圧ラットを用いた新規 NASH 肝発癌モデルの作製−緑茶カテキン EGCG は NASH・高血圧に関連した肝腫瘍形成を抑制する−

岐阜大学医学部附属病院第 1 内科　清水　雅仁

河内　隆宏

7．肝硬変患者におけるサルコペニアの予測因子

岐阜大学医学部附属病院第 1 内科　白木　　亮

華井　竜徳

8．BCAA 摂取、血漿 BCAA 値と糖尿病マーカーとの関連

岐阜大学大学院医学系研究科疫学・予防医学　永田　知里

9．栄養指導ツールの評価

浜松医療センター栄養管理室　岡本　康子

事務局連絡

- 次回総会の日程
- 事務処理について

閉会の挨拶　（17：00 終了予定）

厚生労働科学研究　肝炎等克服緊急対策研究事業

「ウイルス性肝疾患患者の食事・運動療法とアウトカム評価に関する研究」

平成25年度第二回総会プログラム

研究代表者　森脇　久隆　（岐阜大学大学院医学系研究科消化器病態学）

期　日：平成 25 年 12 月 3 日（火）　　14：00-17：00
（13：30 より受付開始）

場　所：安保ホール501AB号室（名古屋市中村区名駅 3-15-9）
TEL(052)561-9831

平成25年度　厚生労働科学研究費補助金　肝炎等克服緊急対策事業
「ウイルス性肝疾患患者の食事・運動療法とアウトカム評価に関する研究」
事務局:岐阜大学大学院医学系研究科消化器病態学
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研究代表者 挨拶（研究代表者　森脇久隆）　14：00 ～ 14：05

肝炎等克服緊急対策研究事業の企画及び評価に関する研究班　挨拶

東芝病院研究部　三代俊治先生　14：05 ～ 14：10

共同研究の経過報告と今後の予定　森脇久隆・白木　亮　14：10 ～ 14：40

個別研究の提案　14：40 ～

（途中　休憩 10 分）

1．慢性肝疾患の糖代謝異常と PEM の検討

兵庫医科大学内科学　肝・胆・膵科　西口　修平

齋藤　正紀

2．「肝硬変患者における体力測定と運動指導の効果」

「サルコペニアと肝癌との関連」

佐賀大学医学部内科学　肝臓・糖尿病・内分泌内科　水田　敏彦

井手　康史

3．肝細胞癌術後再発および生存予後因子としての術前骨格筋脂肪化

関西医科大学外科　海堀　昌樹

4．新規 NAFLD/NASH 関連肝発癌モデルとペントキシフィリンによる発癌抑制効果

岐阜大学医学部附属病院第 1 内科　清水　雅仁

5．BCAA は肝硬変を合併したサルコペニア患者の予後を改善させる

岐阜大学医学部附属病院第1内科　白木　亮

華井　竜徳

6．食習慣と肝臓がん発症リスクとの関連

岐阜大学大学院医学系研究科疫学・予防医学　永田　知里

7．栄養指導ツールの評価

浜松医療センター栄養管理室　岡本　康子

8．レボカルニチン製剤投与中の C 型肝硬変患者（LC-C）における運動療法の有用性（アウトカム評価）

愛知医科大学大学院医学研究科医学教育センター　福澤　嘉孝

事務局連絡

● 事務処理について

閉会の挨拶　（17：00 終了予定）