

## Association of branched-chain amino acid intake trajectory in adulthood with the risk of type 2 diabetes and its related risk factors

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*To the Editor:* Type 2 diabetes (T2D) showed increasing prevalence worldwide and put a huge burden on health-care systems.<sup>[1]</sup> Branched-chain amino acids (BCAAs, including Leucine, Isoleucine, and Valine), a prominent group of essential amino acids, are important nutrition signals that have important effects on protein synthesis, glucose homeostasis, and nutrient-sensitive signaling pathways. Plasma BCAA can predict the development of T2D, whereas the studies of dietary BCAA on T2D risk showed conflicting results.<sup>[2]</sup> Most of the researches about dietary BCAAs used a single or limited number of measurements, ignoring the dynamic changes of dietary BCAA levels throughout life and their relevance to the development of diabetes. A life-course approach using multiple dietary BCAA measurements over time may shed new light on dietary BCAA trajectories and their relation to T2D risk. Therefore, in the current study, we first use latent class mixed model (LCMM) to characterize BCAA intake trajectories over 18 years in longitudinal data from China and investigate the association of BCAA intake trajectories with the risk of T2D and its biomarkers after adjusting for potential confounding factors.

This study included 13,122 participants in the China Health and Nutrition Survey from 1991 to 2011 after excluding participants based on the following criteria: (1) having implausible energy intake, (2) having extreme 1% of outliers for BCAA intake (mg/kcal), (3) receiving only one survey, (4) under 18 years old in the first survey, (5) with diabetes in the first survey, and (6) in pregnant. This study was approved by the Institutional Review Committees of the University of North Carolina at Chapel Hill and the China National Institute of Nutrition and Food Safety. All participants provided written informed consent before the surveys.

Dietary assessment is based on a combination of three consecutive 24 h recall at the individual level, and a food inventory taken at the household level over the same 3-day period. The BCAA content was calculated by the Chinese

Food Composition Table and was expressed as energy density (mg/kcal).

Anthropometric variables were measured at each survey. In the survey of 2009, a 12 mL blood sample was collected after overnight fasting to test blood biochemical indexes, such as serum glucose and hemoglobin A1c (HbA1c).

T2D was identified by self-reports of a history of diabetes diagnosis, and/or fasting blood glucose  $\geq 7.0$  mmol/L, and/or HbA1c  $\geq 40$  mmol/mol (6.5%), and/or receiving treatment for diabetes.

The LCMM was used to identify BCAA intake trajectories using the R package LCMM.<sup>[3]</sup> Cox multivariate regression models were used to estimate the associations between BCAA intake trajectories and T2D risk, with age as the time scale. Time at entry was the age at the beginning of follow-up, and exit time was the age when participants were diagnosed with diabetes, lost to follow-up, or censored at the end of the follow-up period, whichever came first.

General linear models were performed to test differences in baseline characteristics of continuous variables and biomarkers across trajectories.  $\chi^2$  test was used to measure differences in baseline characteristics of classified variables. Subgroup analysis was performed in those having a blood sample taken in 2009 by using the BCAA intake trajectory classes modeled in the total sample. A mediation analysis model performed using R package lavaan was constructed to examine whether the association between BCAA intake trajectories and risk of T2D was mediated by these biomarkers. Statistical analyses were performed using R 3.4.3 and SPSS 23.0 (Beijing, China). A two-sided *P* value  $< 0.05$  was considered statistically significant.

Trajectories of BCAA intake are shown in Figure 1. The first trajectory, labeled “T1: light-stable,” corresponds to

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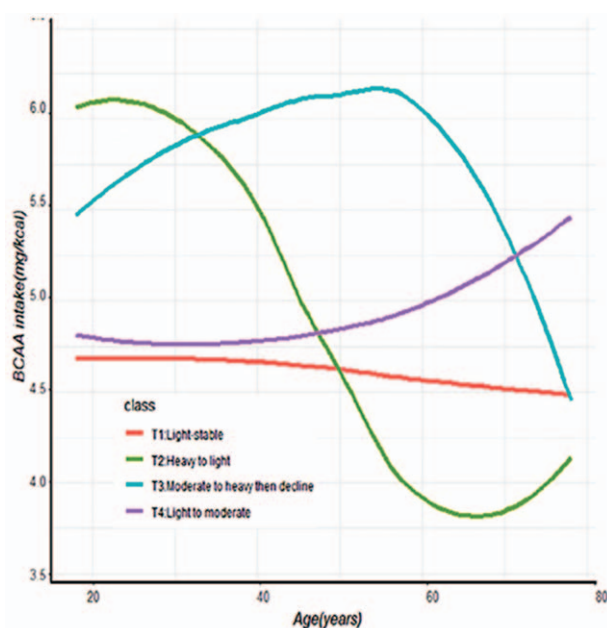
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**Figure 1:** Trajectories of BCAA intake ( $n = 13,122$ ) from the CHNS by LCMM. BCAA: Branched-chain amino acids; CHNS: China Health and Nutrition Survey; LCMM: Latent class mixed model.

people who had stable light intake throughout adulthood. The second trajectory, “T2: heavy to light,” corresponds to people who had heavy intake in early adulthood and then declined to light with age. The third trajectory, “T3: moderate to heavy then decline,” corresponds to people who increased to heavy intake until middle-aged then showed a gradual decline to light with age, “T4: light to moderate,” corresponds to people who increased from light to moderate intake throughout adulthood. These four trajectories were estimated to include 62.6%, 5.1%, 6.6%, and 25.7% of participants, respectively.

The relation between BCAA intake trajectories and T2D risk is presented in Supplementary Table 1, <http://links.lww.com/CM9/A565>. Compared with light-stable BCAA intake, trajectories labeled “T3” and “T4” significantly increased the risk of T2D (HR 1.36 [95% CI 1.04, 1.78] for T3; HR 1.51 [95% CI 1.30, 1.74] for T4) after adjusting for covariates.

The differences for T2D related biomarkers across BCAA intake trajectories are shown in Supplementary Table 2, <http://links.lww.com/CM9/A565>. Total cholesterol ( $P < 0.001$ ), high-density lipoprotein cholesterol (HDL-C) ( $P < 0.001$ ), low-density lipoprotein cholesterol (LDL-C) ( $P = 0.001$ ), triacylglycerol ( $P = 0.023$ ), uric acid ( $P = 0.003$ ), lipoprotein A ( $P = 0.001$ ), and apolipoprotein B ( $P < 0.001$ ) in the two trajectories (T3 and T4) were significantly different with other two trajectory classes (T1 and T2). Fasting glucose, HbA1c in these two trajectories seemed to be non-significant higher than the other two trajectory classes ( $P = 0.51$  and  $0.12$ , respectively).

Mediation effects of total cholesterol, HDL-C, LDL-C, triacylglycerol, and Apolipoprotein B on the association between trajectories and risk of T2D are shown in Supplementary Figure 1, <http://links.lww.com/CM9/>

A565. The total effect of BCAA intake trajectories was estimated at 0.033. The  $\beta_1$  to  $\beta_{10}$  were used to calculate the overall indirect effect for these factors, respectively ( $\beta_{ind} = 0.004$  for total cholesterol, 0.005 for HDL-C, 0.005 for triacylglycerol, and 0.004 for apolipoprotein B; both  $P < 0.05$ ). The percentages of the total effect mediated by total cholesterol, HDL-C, triacylglycerol, and apolipoprotein B (APO-B) were estimated at 12.1%, 15.2%, 15.2%, and 12.1%, respectively.

This study indicated the adverse effect of increasing trend of BCAA intake on T2D risk and related biomarkers, demonstrating the importance of BCAA intervention strategies in early adulthood.

One trajectory mentioned above showed a persistent increase from light to moderate BCAA intake throughout adulthood, emphasizing the unfavorable effects of increasing trend of BCAA intake especially in late adulthood even though with light baseline level and the importance of avoiding rise tendency of BCAA intake over the adult life course. If BCAA intake was heavy in early adulthood, decreasing intake promptly can availably reduce the adverse effect of BCAA like the trajectory that declining from heavy to light continuously showed no significant association with T2D risk. The other trajectory with a high risk of T2D showed that keeping increased levels until middle-aged and then decreasing to light cannot avoid the risk effectively although the risk seemed slightly lower than consistently increased trajectory. Aging is characterized by a progressive loss of physiological integrity, leading to impaired function and increased vulnerability to death, typical hallmarks of aging include progressive loss of skeletal muscle mass, muscular mitochondrial dysfunction, etc.<sup>[4]</sup> Plasma BCAA, which is a credible T2D risk factor, is affected by dietary intake and individual ability of catabolism meanwhile.<sup>[2]</sup> Therefore, it is meaningful to avoid increasing BCAA intake with age, which may show inadequate capacity of BCAA catabolism and clearance, and to decrease from heavy intake level as early as possible to mitigate the risk of T2D notably.

Subgroup analyses suggested that two trajectories with a high risk of T2D were probably associated with higher total cholesterol, LDL-C, triacylglycerol, uric acid, lipoprotein A and apolipoprotein B, and lower HDL-C. Furthermore, total cholesterol, HDL-C, triacylglycerol, and APO-B mediated portion of the association between trajectories and the risk of T2D. Some experimental studies provide the underlying mechanisms of these mediation effects. BCAA supplementation activated hepatic mammalian target of rapamycin (mTOR) and then blocked hepatic transformation-free fatty acids (FFA) to triacylglycerol, resulting in hyperlipidemia. As for in adipocytes, BCAA activated adenosine monophosphate (AMP)-activated protein kinase (AMPK $\alpha$ 2) and stimulated lipolysis, increasing plasma FFAs and leading to accumulation of FFAs in the liver.<sup>[5]</sup> Furthermore, hyperlipidemia has been proved to be associated with T2D through inducing beta-cell dysfunction and insulin resistance in previous studies.

In conclusion, our study emphasizes that increasing BCAA intake throughout the adult life or decreasing since middle-

aged shows unfavorable effect on T2D risk but decreasing intake since early adulthood dose not, underlining that the intervention strategies for BCAA should be timely implemented in early adulthood to avoid the harm effectively. Furthermore, BCAA intake is closely related to various kinds of blood lipid which could predict the further risk of cardiovascular disease. Additional studies are needed to explore the relationship between BCAA intake and cardiovascular disease and to apply these findings widely in public health practice.

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### Conflicts of interest

None.

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