Association between physical activity and liver function - Modulation by Blautia: the CIRCS study

Masanori Nagao (1,2,3)

Masashi Hotta (3), Koji Hosomi (3,4), Takayuki Jujo Sanada (3,5), Kokoro Shirai (6), Narumi Funakubo (2)

Kazumasa Yamagishi (7,8), Yuji Shimizu (9), Isao Muraki (10), Hironori Imano (11), Hinako Nanri (12), Motohiko Miyachi (13)

Haruka Murakami (12,14), Masahiko Kiyama (2,15), Hiroyasu Iso (16), Jun kunisawa (3), Tetsuya Ohira (1,2)

1 : Fukushima Medical University Radiation Medical Science Center for the Fukushima Health Management Survey Office of Epidemiology
2 : Fukushima Medical University School of Medicine/ Department of Epidemiology
3 : National Institutes of Biomedical Innovation, Health and Nutrition/ Microbial Research Center for Health and Medicine/ Laboratory of Vaccine Materials and Laboratory of Gut Environmental System
4 : Osaka Metropolitan University/ Graduate School of Veterinary Science/ Laboratory of Veterinary Epidemiology
5 : International University of Health and Welfare/ Narita Hospital/ Department of Respirology
6 : The University of Osaka Graduate School of Medicine/ Division of Health Science/ Social and Behavioral Medicine
7 : Juntendo University/ Graduate School of Medicine/ Department of Public Health
8 : University of Tsukuba/ Institute of Medicine, and Health Services Research and Development Center/ Department of Public Health Medicine
9 : Osaka Institute of Public Health/ Division of Public Health/ Epidemiology Section
10 : University of Tsukuba/ Institute of Medicine/ Department of Public Health Medicine
11 : Kindai University Faculty of Medicine/ Department of Public Health
12 : National Institutes of Biomedical Innovation, Health and Nutrition/ Center for Clinical Nutrition/ Laboratory of Behavioral Physiology
13 : Waseda University/ Faculty of Sport Sciences
14 : Ritsumeikan University/ College of Sport and Health Science
15 : Institute of Preventive Medicine
16 : Japan Institute for Health Security/ Bureau of Global Health Cooperation/ Institute for Global Health Policy Research

Background : Gut microbiota may influence host metabolism and modify the health effects of lifestyle factors. We examined whether the association between physical activity and liver dysfunction is modified by the abundance of *Blautia*, a bacterium reported to have anti-obesity effects.

Methods : We analyzed data from adults who underwent health checkups (2019–2024) in Akita, Osaka, and Fukushima, Japan. Antibiotic users were excluded. Relative bacterial abundance in stool was assessed via 16S rRNA sequencing. Participants were divided into poor- and rich-Blautia groups based on the median abundance (6.07%). Physical activity was assessed using a questionnaire from the Japan Public Health Center-based Study, covering time spent in strenuous work, standing/walking, and sitting. METs were assigned as 4.5, 2.0, and 1.5, respectively; other activities were also assigned 1.5. Total physical activity (METs-h/day) was calculated by multiplying METs by duration. Liver dysfunction was defined as AST $\geq$ 31 U/L, ALT $\geq$ 31 U/L, or γ-GTP $\geq$ 51 U/L. Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for liver dysfunction per 1-SD (4.3) increase in physical activity, adjusted for sex, age (continuous), smoking/alcohol (never, former, current), and area, and stratified by Blautia group.

Results : Among 914 participants (548 women; mean age: 60.9 years), mean physical activity was 35.6 (SD 4.4) and 35.0 (SD 4.2) METs-h/day in the poor- and rich-Blautia groups, respectively. Liver dysfunction prevalence was 23.6% and 21.0%. Multivariable-adjusted ORs (95%CIs) for liver dysfunction per 1-SD increase in physical activity were 1.10 (0.88–1.38) in the poor-Blautia group and 0.74 (0.57–0.96) in the rich-Blautia group (p for interaction = 0.029).

Conclusion : Higher physical activity was associated with lower prevalence of liver dysfunction in the rich-Blautia group, but not in the poor-Blautia group, suggesting a modifying role of gut microbiota.

Association between Internet use and subsequent depression in Japanese adults by the JPHC-NEXT Study

Yasuko Kikuchi (1)

Zui C Narita (2,16), Hisateru Tachimori (3,4), Kazumasa Yamagishi (5), Nobufumi Yasuda (6), Isao Saito (7)

Kazuhiko Arima (8), Kozo Tanno (9), Taiki Yamaji (10), Motoki Iwasaki (10), Manami Inoue (11), Shoichiro Tsugane (12)

Norie Sawada (1)

1 : Division of Cohort Research, National Cancer Center, Japan, Institute for Cancer Control, Tokyo, Japan.
2 : Department of Behavioral Medicine, National Institute of Mental Health, National Center of Neurology and Psychiatry, Tokyo, Japan.
3 : Department of Information Medicine, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Tokyo, Japan
4 : Department of Health Policy and Management, Keio University School of Medicine, Tokyo, Japan
5 : Department of Public Health, Juntendo University School of Medicine, Tokyo, Japan
6 : Department of Public Health, Kochi University Medical School, Kochi, Japan
7 : Division of Life Span Development and Clinical Psychology, Graduate School of Education, Ehime University, Matsuyama, Ehime, Japan
8 : Department of Public Health, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
9 : Department of Hygiene and Preventive Medicine, School of Medicine, Iwate Medical University, Iwate, Japan
10 : Division of Epidemiology, National Cancer Center Institute for Cancer Control, Tokyo, Japan
11 : Division of Prevention, National Cancer Center Institute for Cancer Control, Tokyo, Japan
12 : Graduate School of Public Health, International University of Health and Welfare, Tokyo, Japan

Background : As the Internet has become widely used across various age groups, increasing attention has been paid to health issues associated with its use, particularly mental health concerns. Some studies have reported a protective relationship between Internet use and depressive symptoms in adult generations. However, there are still divergent perspectives that remain inconclusive.

Methods : We conducted a prospective study based on a 5-year longitudinal survey of the Japan Public Health Center-based Prospective Study for the Next Generation (JPHC-NEXT), for 56387 participants aged 40 to 74 years who had no depression history at baseline survey. We examined the association between weekly Internet use frequency, daily Internet use duration, and 5-year risk of depression using a self-reported questionnaire. The relationship between Internet use and depression was analyzed using multivariable logistic regression.

Results : Compared to non-users, daily Internet use was associated with a lower odds ratio (OR) for depression at 5 years (OR:0.91, 95% CI: 0.84-0.98). Regarding Internet use time, individuals using the Internet for less than 2 hours per day had a lower OR for depression compared to non-users (OR:0.92, 95% CI: 0.86-0.985). Furthermore, when combining frequency and duration of Internet use into four categories-high frequency (>5 days per week) /long duration (3 hours/day or more), high frequency/ short duration (2hours/day or less), low frequency (3-4 days/week or less)/ long duration, and low frequency/short duration-using the low frequency/short duration group as the reference, the high frequency/short duration tended to show a lower OR for depression (OR:0.95, 95% CI:0.88-1.02), albeit without statistical significance.

Conclusions : Though we could not clarify the significant difference, the frequent but brief Internet use may be associated with a lower risk of subsequent depression.

School Connectedness and Trends of Adolescent Health-Risk Behaviors: Repeated Cross-Sectional Study

Minoru Takakura (1,2)

Akira Kyan (2,3), Masaya Miyagi (4)

1 : Graduate School of Sports and Health Sciences, Meio University
2 : Faculty of Medicine, University of the Ryukyus
3 : Center for Social Common Capital beyond 2050, Kyoto University
4 : Faculty of Education, University of the Ryukyus

Background : Recent global evidence indicates that many adolescent health-risk behaviors (HRBs) have declined over time. Within the social determinants of health framework, psychosocial environments—particularly in schools, the primary adolescent community—play a crucial role. School connectedness (SC) has consistently been identified as a protective factor for youth health and health-related behavior. However, limited research has examined how temporal changes in SC may account for secular trends in adolescent HRBs. We hypothesized that improvements in HRBs could be explained by (a) changes in the protective association between SC and HRBs and/or (b) changes in exposure to SC over time.

Objective : To investigate associations between temporal trends in adolescent HRBs and changes in SC.

Methods : We analyzed data from five repeated cross-sectional surveys (2008–2024) of 12,047 public high school students in Okinawa, Japan. HRBs included current smoking, current drinking, and sexual experience. SC was measured using the Rasmussen scale (EJPH, 2005). Gender-stratified Poisson regression models with cluster-robust standard errors estimated (a) moderation (interaction between survey year and SC) and (b) mediation effects of SC on time trends, adjusting for the relevant covariates.

Results : From 2008 to 2024, the prevalence of all HRBs significantly declined, while mean SC scores significantly increased for both boys and girls. SC was consistently protective against all HRBs, and this association remained stable over time (no significant interaction). Mediation analyses revealed significant indirect effects of SC, whereby increases in SC partially explained reductions in HRBs over time.

Conclusions : The rising levels of SC have contributed to improvements in adolescent HRBs over the past 16 years. Strengthening SC may be a key strategy in sustaining favorable behavioral trends among adolescents.

Association of equol-producing status with cerebrovascular lesions in Japanese women

Rani Baroi Ritu (1)

Keiko Kondo (1), Yukiko Okami (2), Akira Sekikawa (3), Akira Fujiyoshi (4), Aya Kadota (1), Sayuki Torii (1), Rajib Mondal (1)
Megumi Kawashima (1), Takashi Hisamatsu (5), Satoshi Shitara (6), Maya Oki (7), Kazumichi Yoshida (6)
Yoshiyuki Watanabei (7), Katsuyuki Miura (1)

1 : Department of Preventive Medicine, NCD Epidemiology Research Center, Shiga University of Medical Science, Otsu, Japan
2 : Gunma University Center for Food Science and Wellness, Gunma, Japan
3 : Department of Epidemiology, School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA
4 : Department of Hygiene, Wakayama Medical University, Wakayama, Japan
5 : Department of Public Health, Shiga University of Medical Science, Otsu, Shiga, Japan
6 : Department of Neurosurgery, Shiga University of Medical Science, Otsu, Shiga, Japan
7 : Department of Radiology, Shiga University of Medical Science, Otsu, Shiga, Japan

Background : Equol, a metabolite of soy isoflavone daidzein, improves vascular health via antioxidative and anti-inflammatory effects through strong binding to estrogen receptor β. Previous reports have shown that equol producers had a significantly lower burden of aortic calcification. However, its relationship with cerebral small vessel diseases (CSVD) and cerebral large artery stenosis (CLAS) is not clarified.

Objectives : We aimed to investigate the association of equol-producing status with CSVD and CLAS in Japanese women.

Methods : We cross-sectionally analyzed data from 590 women in the Shiga Epidemiological Study of Subclinical Atherosclerosis (SESSA). Urinary and serum concentrations of daidzein and equol were measured using HPLC system. Equol producers were defined as individuals with $\log_{10}$ (urinary equol-to-daidzein) $\geq$ -1.30 or (serum equol-to-daidzein) $\geq$ -1.42. Magnetic resonance imaging of the brain was used to assess the presence of CSVD (deep and subcortical white matter hyperintensities, periventricular hyperintensities, lacunar infarcts, and microbleeds) and CLAS. Each CSVD feature was assigned one point, and CSVD was defined as a total score of $\geq$1. We used multivariable modified Poisson regression analysis to estimate relative risk (RR) and 95% confidence intervals (CI) of prevalent CSVD and CLAS according to equol-producing status. Covariates included age, body mass index, smoking, alcohol consumption, diabetes mellitus, dyslipidemia, and hypertension.

Results : Participants (mean$\pm$SD age 74.1$\pm$5.4 years) had a prevalence of CSVD and CLAS of 48.0% and 33.6%, respectively. Equol producers (41.4%) had a significantly lower risk of CSVD (RR [95% CI], 0.81 [0.69–0.96]) and CLAS (RR [95% CI], 0.79 [0.63–0.99]) after being adjusted for covariates, compared to equol non-producers.

Conclusions : Equol producers exhibited a lower risk of CSVD and CLAS among Japanese women, suggesting a potential protective role of equol in cerebrovascular health.

Estimation of risk ratios for mortality during compulsory education by birth month in Japan

Yohei Ono (1)

Tsuguhiko Kato (2), Yuki Yonekura (3), Nobuo Nishi (2)

1 : St. Luke's International University, Graduate School of Public Health, Division of Biostatistics and Bioinformatics
2 : St. Luke's International University, Graduate School of Public Health, Division of Health Policy and Management
3 : St. Luke's International University, Graduate School of Nursing Science, Department of Nursing Informatics

Background : In Japan, compulsory education is nine years in total: six years in elementary school and three years in junior high school. All children aged six years enter the period on Apr 1 every year with almost one year difference of age. The impact of such a relative age on children should be investigated not only in their academic achievements but also in their behavioral and health outcomes.

Objective : This study aimed to estimate risk ratios (RRs) of morality during the period by birth month in Japan.

Methods : We obtained approval of on-site use of death records of the Vital Statistics from 2001 to 2022 by applying to e-Micro of the National Statistics Center. Birth months were divided into four terms: Apr to Jun (T1), Jul to Sep (T2) and Oct to Dec (T3) in the same year and Jan to Mar (T4) in the next year. Mortality risk was calculated as the sum of the number of deaths from six to 15 years of age divided by the sum of the number of children who survived until the year to five years of age. We calculated RRs of mortality with 95% confidence intervals (95% CI) for T2, T3 and T4 in reference to T1 in two methods. The first method used chronological age (CA) and the second method used school age (SA) where all children in the same school year were assigned the same age as had on its first day (Apr 1).

Results : The numbers of deaths from 2008 to 2022 were 1193 for T1, 1276 for T2, 1274 for T3 and 1227 for T4 in CA, and 1190 for T1, 1303 for T2, 1289 for T3 and 1220 for T4 in SA. RRs of mortality (95% CI) for T2, T3 and T4 were not significant from T1 when CA was used: 1.01 (0.94 – 1.10) for T2, 1.04 (0.96 – 1.12) for T3 and 1.05 (0.97 – 1.14) for T4; or SA was used: 1.04 (0.96 – 1.12) for T2, 1.07 (0.99 – 1.16) for T3 and 1.05 (0.97 – 1.13) for T4.

Discussion and Conclusion : The difference in mortality by birth month was not observed during the compulsory education in our data. Further investigations are needed, adjusting differences in birth cohort.