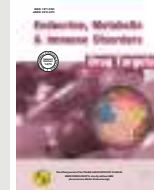**RESEARCH ARTICLE**

Tobacco Smoking and Association between Betel Nut Chewing and Metabolic Abnormalities Among Military Males: The CHIEF Study

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Abstract: *Aim:* To investigate the effect of smoking and alcohol intake on the association between betel nut chewing and each metabolic abnormality.

Background: Betel nut chewing has been associated with metabolic syndrome.

Objective: Whether the association is affected by tobacco or alcohol use is not clarified so far.

Methods: The authors conducted a cross-sectional study using 6,657 military males, aged 18-50 years in eastern Taiwan in 2013-2014. Metabolic syndrome was defined according to the International Diabetes Federation's ethnic criteria for Asians. The population was classified as non-betel nut chewers (N =5,749), current chewers with both tobacco and alcohol use (N =615), and current chewers without tobacco and/or alcohol use (N =293). Multiple logistic regression analyses were stepwise adjusted for the confounders including alcohol and tobacco use to determine the association of betel chewing with the metabolic abnormalities.

Results: As compared to the non-current chewers, the current chewers with both tobacco/alcohol use and those without had a higher risk of metabolic syndrome (odds ratios (OR) and 95% confidence intervals: 2.46 (2.00-3.02), and 2.04 (1.53-2.73), respectively) after controlling for age, service specialty, total cholesterol levels ≥200 mg/dL and exercise frequency (model 1). The association did not change much in the two chewing groups after additionally adjusting for alcohol consumption (model 2) (OR: 2.49 (1.99-3.12), and 2.04 (1.52-2.73), respectively), whereas the relationship reduced significantly in the chewers with both tobacco/alcohol use rather than those without after further adjusting for smoking (model 3) (OR: 2.18 (1.71-2.78) and 2.02 (1.51-2.71), respectively). This was in parallel with the pattern for the association of betel nut chewing with serum triglycerides >150 mg/dL in the chewers with both tobacco/alcohol use and those without in model 1 (OR: 2.90 (2.40-3.51) and 1.90 (1.45-2.49), respectively, p =0.011), in model 2 (OR: 2.82 (2.30-3.46) and 1.89 (1.44-2.49), respectively, p =0.040), and in model 3 (2.26 (1.81-2.81) and 1.87 (1.42-2.45), respectively, p =0.76).

Conclusion: Our findings suggest that tobacco smoking but not alcohol intake could increase the relationship of betel nut chewing with metabolic syndrome, which is likely mediated by a synergic effect on increasing serum triglycerides levels.

1. INTRODUCTION

Areca nut, also called betel nut, is prevalent in the tropical regions of the Pacific and Southeast Asia, and parts of East Africa [1]. Areca nut is the seed of areca palm consisting of various toxic compounds, and for instance arecoline, one of the primary psychoactive ingredients in the nut, can result in oral mucosa histologic changes such as submucosal fibrosis and malignancies [2, 3]. Betel nut chewing is the fourth most popular unhealthy habit in the world after tobacco, alcohol, and caffeine consumption [4]. Most of the betel nut chewers reside in Asia [1]. However, with the increasing

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number of Asian immigrants in Europe and North America, betel nut consumption has become a global health problem. In sum, there are about 600 million individuals consuming betel nut globally [2]. Two epidemiologic studies reveal that betel nut adult chewers range between 12.2% and 16.5% of the general population in Taiwan [3, 5] In addition, the prevalence of betel nut chewing in the military of Taiwan was estimated from 20% to 25% during 2001-2004, which was higher than that in the general population, indicating that this toxic agent has posed more risks to the health of the military personnel [6].

Metabolic syndrome is characterized by abdominal obesity, prehypertension, prediabetes, and dyslipidemia [7]. Previous studies have shown that metabolic syndrome is associated with a higher risk of incident diabetes, cardiovascular disease, and the related or overall mortality [8-10]. The prevalence of metabolic syndrome has affected approximately 20–30% of the adult individuals in most developing countries [11, 12]. Several metabolic abnormalities such as obesity and hyperglycemia related to insulin resistance by betel nut chewing have been reported [13]. In addition, the immediate impact of betel nut chewing on cardiovascular system includes tachyarrhythmia and blood pressure elevation [14]. In Taiwan, the prevalence of diabetes and metabolic syndrome was 1.3-fold and 1.9-fold higher in betel nut chewers as compared to non-chewers [15, 16].

To the best of our knowledge, more than 90% of the betel nut chewers are males and would consume tobacco or alcohol beverages simultaneously [17, 18]. Although a prior study has revealed that the betel nut chewers with active smoking might have a higher risk of metabolic syndrome than those without, we noticed that the study was flawed without an adjustment for the status of alcohol intake in the model [19]. Tobacco smoking influences arterial blood pressure, and plasma lipid and glucose metabolism [20-22], resulting in an impairment of physical fitness and visceral fat accumulations [23, 24]. However, the effect of alcohol consumption on metabolic disorders is not consistent. For instance, moderate alcohol intake has been associated with lower blood pressure, higher high-density lipoprotein, and lower plasma C-reactive protein in some cohort studies [25-27]. Therefore, the purpose of the study is to investigate the association of betel nut chewing with metabolic syndrome and related components, and clarify if alcohol intake and tobacco smoking are modifiers for this relationship.

2. METHODS

2.1. Study Population

This study used the cardiorespiratory fitness and hospitalization events in armed forces (CHIEF) population in 2013-2014 [28]. There were 9,076 military participants enrolled in the annual health examinations of the Hualien Armed Forces General Hospital, the only military referral center in Hualien, Taiwan. Female participants (N =766) were excluded for a very low prevalence of betel nut chewing (1.3%) and those with missing relevant data (N =1,653)

were further excluded, leaving a total of 6,657 male subjects, with ages between 18 and 50 years, for the analysis. The study design has been described in detail previously [29-33]. Each participant self-reported a questionnaire for demographic information and medical history including the status of tobacco smoking, alcohol intake and betel nut chewing (current versus former and never). Anthropometrics including body height, body weight and waist circumference were measured in standing position. Body height and body weight were measured without wearing shoes and heavy clothes. Body mass index (BMI) was calculated as the ratio of weight (kilograms) to the square of height (meters). Measurement of waist circumference was performed at the midway between the lower rib margin and iliac crest. Arterial blood pressures were measured once over the right upper arm at sitting position, with a break for 15 minutes or longer by the automatic blood pressure monitor (FT-201, Parama-Tech Co Ltd, Fukuoka, Japan). Overnight fasting blood samples were collected to measure fasting plasma glucose, triglycerides, total cholesterol and high-density lipoprotein. According to the status of betel nut chewing, tobacco smoking, and alcohol intake, the male subjects were classified into 3 groups including the non-betel nut chewers, the betel nut chewers without tobacco and/or alcohol use, and the chewers with both tobacco and alcohol use.

2.2. Definition of Metabolic Syndrome

Metabolic syndrome was defined according to the International Diabetes Federation ethnic criteria for Asians, as the presence of three or more of the following features: (1) central obesity: waist circumference ≥90 cm in males; (2) elevated fasting serum triglycerides ≥150 mg/dL or on lipid-lowering therapy; (3) decreased fasting high-density lipoprotein cholesterol <40 mg/dL in males or on lipid-lowering therapy; (4) elevated systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg or on antihypertensive therapy; (5) elevated fasting plasma glucose ≥100 mg/dL or on antidiabetic therapy [11]. This definition is in line with the modified NCEP ATP III definition [34].

2.3. Data Analysis

Continuous variables and categorical variables were expressed as mean with standard deviation and number (percentage), respectively. Independent two-sample t-test and chi-square test were used to examine differences in continuous variables and categorical variables between groups, respectively. Multiple logistic regressions were used to determine the association of betel nut chewing status with metabolic syndrome and its components. Cochran-Armitage test was used to examine the linear trend. In model 1, age, service specialty, total cholesterol levels ≥200 mg/dL and exercise frequency were adjusted. In model 2, alcohol intake status was additionally adjusted. In model 3, tobacco smoking status was further adjusted. A value of p <0.05 was considered significant. Statistical analyses were performed with a standard program (Statistical Package for Social Sciences, SPSS, version 25.0).

3. RESULTS

3.1. Subject Characteristics

The characteristics of the male subjects in each group are shown in Table **1**. In the overall cohort, there were 5,749 non-betel nut chewers (86.3%) and 908 current betel nut chewers (13.7%). Of the betel nut chewers, 293 participants (4.4%) did not consume tobacco and/or alcohol beverages (22 with betel nut chewing only (0.3%), 114 with smoking and without alcohol intake (1.7%), and 157 with alcohol intake and without smoking (2.4%)) and 615 participants (9.2%) concomitantly consumed tobacco and alcohol beverages. As compared to the non-chewers, the current betel nut chewers had a higher prevalence of metabolic abnormalities, tobacco smoking and alcohol consumption, and lower exercise frequency. However, there was a similar prevalence of metabolic abnormalities and exercise frequency between the betel nut chewers with both tobacco and alcohol use and the chewers without. The prevalence of metabolic syndrome stratified by ages is shown in Table **2**. As compared to the non-chewers, the chewers had higher metabolic syndrome prevalence in each age category defined by approximately 10-year interval: 18-27, 28-37, and 38-50 years.

Table 1. Descriptive characteristics of the study cohort based on betel nut chewing status.

-	-	Betel Nut Chewer (n=908)		-
Characteristics	**Non-chewer (n=5,749)**	**Betel Nut Without Tobacco and/or Alcohol Use (n=293)**	**Betel Nut With Tobacco and Alcohol Use (n=615)**	***p*-value**
Age (years old)	29.04 ± 5.97	29.57 ± 5.84	28.71 ± 5.87	0.12
Specialty (%)	-	-	-	-
Air force	4508 (78.4)	209 (71.3)	466 (75.8)	<0.01
Army	1137 (19.8)	83 (28.3)	149 (24.2)	-
Navy	104 (1.8)	1 (0.3)	0 (0.0)	-
Body mass index, BMI (kg/m^2)	25.04 ± 3.56	26.62 ± 4.27	26.36 ± 4.16	<0.01
Waist circumference ≥90 (cm)	1506 (26.2)	122 (41.6)	246 (40.0)	<0.01
Blood pressure ≥130/85 mmHg	1411 (24.5)	98 (33.4)	184 (29.9)	<0.01
Total cholesterol ≥200 (mg/dL)	1168 (20.3)	85 (29.0)	142 (23.1)	<0.01
Triglycerides ≥150 (mg/dL)	1095 (19.0)	100 (34.1)	239 (38.9)	<0.01
Fasting glucose ≥100 (mg/dL)	859 (14.9)	61 (20.8)	116 (18.9)	<0.01
HDL-C <40 (mg/dL)	1099 (19.1)	87 (29.7)	181 (29.4)	<0.01
Current alcohol intake	2452 (42.7)	157 (53.6)	615 (100)	<0.01
Current tobacco smoking	1731 (30.1)	114 (38.9)	613 (100)	-
Exercise frequency	-	-	-	-
Never or occasionally	1115 (19.4)	81 (27.8)	166 (27.0)	<0.01
1-2 times / week	2265 (39.4)	101 (34.6)	206 (33.6)	-
≥3-5 times / week	2362 (41.1)	110 (37.7)	242 (39.4)	-

Continuous variables are expressed as mean ± SD and categorical variables as n (%). HDL-C, high-density lipoprotein cholesterol.

Table 2. Prevalence of metabolic syndrome stratified by age and by betel nut chewing status.

Age	Non-chewers			Betel Nut chewers							
-	-	-	-	Betel Without Tobacco and/or Alcohol Use				Betel with Both Tobacco and Alcohol Use			
-	**Total Subjects**	**With MtS**	**Prevalence (%)**	**Total Subjects**	**With MtS**	**Prevalence (%)**	***p*-value**	**Total subjects**	**With MtS**	**Prevalence (%)**	***p*-value**
18 - 27	2441	161	6.6	112	18	16.1	<0.01	288	41	14.2	<0.01
28 - 37	2850	469	16.5	156	47	30.1	<0.01	286	104	36.4	<0.01
38 - 50	458	111	24.2	25	10	40.0	0.07	41	17	41.5	0.01
Total	5749	741	12.9	293	75	25.6	<0.01	615	162	26.3	<0.01

Abbreviations: metabolic syndrome, MetS All *p*-values were compared between betel nut chewers and the non-chewers groups by t-test.

Table 3. Multiple logistic regression analysis with betel nut chewing status for metabolic syndrome.

-	-	Model 1	-	Model 2	-	Model 3
-	OR	95% CI	OR	95% CI	OR	95% CI
Non-chewer	1.00	-	-	1.00	-	1.00
Betel nut chewer	-	-	-	-	-	-
Without tobacco and/or alcohol use	2.04**	1.53 – 2.73	2.04**	1.52 – 2.73	2.02**	1.51 – 2.71
With tobacco and alcohol use	2.46**	2.00 – 3.02	2.49**	1.99 – 3.12	2.18**	1.71 – 2.78
P-value for trend	-	<0.01	-	<0.01	-	<0.01

Data are presented as odds ratios (OR) and 95% confidence intervals (CI) using multiple logistic regression analysis for Model 1: Adjusted for age, service specialty, total cholesterol ≥200 mg/dL and exercise frequency; Model 2: Adjusted for age, service specialty, total cholesterol ≥200 mg/dL, exercise frequency and current alcohol intake; Model 3: Adjusted for age, service specialty, total cholesterol ≥200 mg/dL, exercise frequency, current alcohol intake and tobacco smoking. Cochran-Armitage test was used to examine p-value for trend *p-value <0.05; **p-value <0.01

Table 4. Multivariable logistic regression analysis models with betel nut chewing status for metabolic syndrome components.

-	-	Model 1	-	Model 2	-	Model 3
-	OR	95% CI	OR	95% CI	OR	95% CI
Non-chewer	1.00	-	1.00	-	1.00	-
Betel nut chewer	-	-	-	-	-	-
Without tobacco and/or alcohol use	-	-	-	-	-	-
Waist circumference ≥90 cm	1.86**	1.45 – 2.38	1.84**	1.43 – 2.37	1.85**	1.43 – 2.37
High blood pressure ≥130/85 mmHg	1.38*	1.07 – 1.79	1.35*	1.04 – 1.75	1.36*	1.05 – 1.77
Serum triglycerides ≥150 mg/dL	1.90**†	1.45 – 2.49	1.89**§	1.44 – 2.49	1.87**	1.42 – 2.45
Fasting glucose ≥100 mg/dL	1.39*	1.03 – 1.88	1.41*	1.04 – 1.91	1.41*	1.05 – 1.91
Serum HDL <40 mg/dL	1.72**	1.33 – 2.24	1.74**	1.34 – 2.27	1.69**	1.29 – 2.21
With both tobacco and alcohol use	-	-	-	-	-	-
Waist circumference ≥90 cm	1.89**	1.58 – 2.26	1.92**	1.58 – 2.32	1.90**	1.55 – 2.33
High blood pressure ≥130/85 mmHg	1.30**	1.08 – 1.57	1.26*	1.03 – 1.53	1.38**	1.12 – 1.71
Serum triglycerides ≥150 mg/dL	2.90**†	2.40 – 3.51	2.82**§	2.30 – 3.46	2.26**	1.81 – 2.81
Fasting glucose ≥100 mg/dL	1.33*	1.07 – 1.66	1.38**	1.09 – 1.75	1.39*	1.08 – 1.79
Serum HDL <40 mg/dL	1.75**	1.45 – 2.11	1.93**	1.57 – 2.36	1.51**	1.22 – 1.88

Data are presented as odds ratios (OR) and 95% confidence intervals (CI) using multiple logistic regression analysis for Model 1: Adjusted for age, service specialty, total cholesterol ≥200 mg/dL and exercise frequency; Model 2: Adjusted for age, service specialty, total cholesterol ≥200 mg/dL, exercise frequency and current alcohol intake; Model 3: Adjusted for age, service specialty, total cholesterol ≥200 mg/dL, exercise frequency, current alcohol intake and tobacco smoking. *p <0.05; **p <0.01. †p =0.01 and §p =0.04 for the difference in OR of serum triglycerides between the two betel chewer groups.

3.2. Multiple Logistic Regressions

The results of multiple logistic regression analyses of betel nut chewing with metabolic syndrome and the components are shown in Tables **3** and **4**, respectively. Table **3** shows that as compared to the non-chewers, the betel nut chewers with both tobacco and alcohol use and those without had a higher risk of metabolic syndrome (odds ratios (OR) and 95% confidence intervals: 2.46 (2.00-3.02), and 2.04 (1.53-2.73), respectively) after the adjustments for the covariates in model 1. The association did not change much in the two betel nut chewing groups after additionally adjusting for alcohol consumption in model 2 (OR: 2.49 (1.99-3.12), and 2.04 (1.52-2.73), respectively), whereas the relationship reduced significantly in the chewers with tobacco and alcohol use rather than those without after further ad-

justing for smoking in model 3 (OR: 2.18 (1.71-2.78) and 2.02 (1.51-2.71), respectively). All p values for trend were significant (p <0.01) in models 1-3. This was in parallel with the pattern for the association between betel nut chewing and high serum triglycerides >150 mg/dL which was the strongest among the five metabolic abnormalities in the chewers with both tobacco and alcohol use and those without in model 1 (OR: 2.90 (2.40-3.51) and 1.90 (1.45-2.49), respectively, p =0.011), in model 2 (OR: 2.82 (2.30-3.46) and 1.89 (1.44-2.49), respectively, p =0.040), and in model 3 (2.26 (1.81-2.81) and 1.87 (1.42-2.45), respectively, p =0.76) (Table **4**). For the other metabolic abnormalities, the association with betel nut chewing did not differ between those with and those without tobacco and alcohol use in models 1-3.

4. DISCUSSION

Our principal findings were that betel nut chewing was associated with a higher risk of metabolic syndrome and its components. The betel nut chewers with both tobacco and alcohol use had the highest 2.5-fold increased risk of metabolic syndrome, followed by the chewers without tobacco or alcohol use with a two-fold increased higher risk of metabolic syndrome as compared to the non-chewers. In addition, betel nut chewing was also associated with each component of metabolic syndrome. The strongest association of betel nut chewing was with high serum triglycerides, particularly for the chewers with both tobacco and alcohol use. Notably, tobacco smoking but not alcohol intake could reduce the difference much in the association between the chewers with and without tobacco and alcohol use, suggesting that current tobacco smoking might be a mediator of betel nut use for metabolic abnormalities.

As stated previously, many hazardous ingredients in betel nut could lead to insulin resistance, blood pressure elevation and abnormal lipid profiles in the body, and thus increase the risk of metabolic syndrome [13, 14]. Our study further confirmed the relationships of betel nut consumption with each metabolic risk factor and metabolic syndrome, which remained significant after adjusting for potential confounders including physical activity, alcohol intake and tobacco smoking. In addition, we found that alcohol consumption did not modify the betel nut association for each metabolic risk factor. Saravanan and Pugalendi have shown that co-administration of betel nut extracts and ethanol to rats could increase blood glucose and lower plasma cholesterol and triglycerides concentrations when compared to ethanol-treated rats, despite unknown mechanisms [35]. Their finding was compatible with our results that there might have a protective effect of betel nut against the alcohol toxicity on elevating plasma lipids concentrations. By contrast, tobacco smoking has been reported with an independent adverse effect on elevating plasma triglycerides levels [36] and might have a synergic effect along with betel nut chewing to increase the risk of metabolic syndrome.

Our study had several advantages. First, all the laboratory examinations were performed in a strict manner and the procedures were standardized. Second, this study included a large number of participants, which may provide sufficient power to detect differences between groups despite heterogeneous categorizations. Third, the degree of multicollinearity among these unhealthy behaviors (betel nut chewing, smoking, and alcohol intake) was low (variance inflation factors: 1.007-1.20) and the associations with metabolic abnormalities should be reliable after stepwise adjustments (supplemental tables). Fourth, since the daily life schedule of military personnel such as physical training and diet consumption would be unified, many unmeasured confounders had been controlled at baseline. In contrast, there were several limitations to our study. First, this study used a cross-sectional design, which restricts the causal inference between the betel nut chewing status and metabolic abnormalities. Second, the study included only male participants and the gen-

eralization of the results to a female population would be restricted. Third, the study population was limited to military members of Taiwan; therefore, the results might not be applied to the general public. Fourth, the amount and length of betel nut chewing, tobacco smoking, and alcohol intake were not quantified and thus we could not clarify the dose-response relationships for metabolic syndrome and the components, despite that the hazardous exposures in young adults were relatively short.

CONCLUSION

In conclusion, our findings reconfirmed that betel nut consumption was associated with a higher risk of metabolic syndrome and its components, and further suggested that tobacco smoking but not alcohol intake might have a synergic effect on betel nut that could increase the relationship with metabolic syndrome, which is likely mediated by increasing serum triglycerides levels.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Institutional Review Broad of Mennonite Christian Hospital (Number: 16-05-008), Hualien, Taiwan.

HUMAN AND ANIMAL RIGHTS

No animals were used in the study. All human procedures were followed in accordance with the Helsinki Declaration of 1975 as revised in 2013 (http://ethics.iit.edu/ecodes/node/3931).

CONSENT FOR PUBLICATION

A written informed consent was obtained from all patients prior to the publication of the study.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflicts of interest, financial or otherwise.

REFERENCES

[1]   Gupta, P.C.; Warnakulasuriya, S. Global epidemiology of areca nut usage. *Addict. Biol.,* **2002**, *7*(1), 77-83.
      http://dx.doi.org/10.1080/13556210020091437 PMID: 11900626
[2]   Gupta, P.C.; Ray, C.S. Epidemiology of betel quid usage. *Ann. Acad. Med. Singapore,* **2004**, *33*(Suppl. 4), 31-36.

PMID: 15389304

[3]   Ko, Y.C.; Chiang, T.A.; Chang, S.J.; Hsieh, S.F. Prevalence of be-tel quid chewing habit in Taiwan and related sociodemographic factors. *J. Oral Pathol. Med.,* **1992**, *21*(6), 261-264.
http://dx.doi.org/10.1111/j.1600-0714.1992.tb01007.x   PMID: 1501158

[4]   Winstock, A. Areca nut-abuse liability, dependence and public health. *Addict. Biol.,* **2002**, *7*(1), 133-138.
http://dx.doi.org/10.1080/13556210120091509 PMID: 11900633

[5]   Wang, L.Y.; You, S.L.; Lu, S.N.; Ho, H.C.; Wu, M.H.; Sun, C.A.; Yang, H.I.; Chien-Jen, C. Risk of hepatocellular carcinoma and habits of alcohol drinking, betel quid chewing and cigarette smok-ing: a cohort of 2416 HBsAg-seropositive and 9421 HB-sAg-seronegative male residents in Taiwan. *Cancer Causes Con-trol,* **2003**, *14*(3), 241-250.
http://dx.doi.org/10.1023/A:1023636619477 PMID: 12814203

[6]   Fernández, I.; Canet, O.; Giné-Garriga, M. Assessment of physi-cal activity levels, fitness and perceived barriers to physical activi-ty practice in adolescents: cross-sectional study. *Eur. J. Pediatr.,* **2017**, *176*(1), 57-65.
http://dx.doi.org/10.1007/s00431-016-2809-4 PMID: 27858223

[7]   Alberti, K.G.; Eckel, R.H.; Grundy, S.M.; Zimmet, P.Z.; Cleeman, J.I.; Donato, K.A.; Fruchart, J.C.; James, W.P.; Loria, C.M.; Smith, S.C. Jr. A joint interim statement of the International Dia-betes Federation Task Force on Epidemiology and Prevention; Na-tional Heart, Lung, and Blood Institute; American Heart Associa-tion; World Heart Federation; International Atherosclerosis Socie-ty; and International Association for the study of obesity. *Circula-tion,* **2009**, *120*(16), 1640-1645.
http://dx.doi.org/10.1161/CIRCULATIONAHA.109.192644
PMID: 19805654

[8]   Galassi, A.; Reynolds, K.; He, J. Metabolic syndrome and risk of cardiovascular disease: A meta-analysis. *Am. J. Med.,* **2006**, *119*(10), 812-819.
http://dx.doi.org/10.1016/j.amjmed.2006.02.031 PMID: 17000207

[9]   Ford, E.S.; Li, C.; Sattar, N. Metabolic syndrome and incident dia-betes: current state of the evidence. *Diabetes Care,* **2008**, *31*(9), 1898-1904.
http://dx.doi.org/10.2337/dc08-0423 PMID: 18591398

[10]   Cho, Y.K.; Kang, Y.M.; Yoo, J.H.; Lee, J.; Lee, S.E.; Yang, D.H.; Kang, J.W.; Park, J.Y.; Jung, C.H.; Kim, H.K.; Lee, W.J. The im-pact of non-alcoholic fatty liver disease and metabolic syndrome on the progression of coronary artery calcification. *Sci. Rep.,* **2018**, *8*(1), 12004.
http://dx.doi.org/10.1038/s41598-018-30465-y PMID: 30104707

[11]   Grundy, S.M.; Brewer, H.B. Jr.; Cleeman, J.I.; Smith, S.C., Jr; Lenfant, C. American Heart Association; National Heart, Lung, and Blood Institute. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart As-sociation conference on scientific issues related to definition. *Cir-culation,* **2004**, *109*(3), 433-438.
http://dx.doi.org/10.1161/01.CIR.0000111245.75752.C6 PMID: 14744958

[12]   Gu, D.; Reynolds, K.; Wu, X.; Chen, J.; Duan, X.; Reynolds, R.F.; Whelton, P.K.; He, J. InterASIA collaborative group. Prevalence of the metabolic syndrome and overweight among adults in China. *Lancet,* **2005**, *365*(9468), 1398-1405.
http://dx.doi.org/10.1016/S0140-6736(05)66375-1   PMID: 15836888

[13]   Hsu, H.F.; Tsou, T.C.; Chao, H.R.; Shy, C.G.; Kuo, Y.T.; Tsai, F.Y.; Yeh, S.C.; Ko, Y.C. Effects of arecoline on adipogenesis, lipolysis, and glucose uptake of adipocytes-A possible role of betel-quid chewing in metabolic syndrome. *Toxicol. Appl. Phar-macol.,* **2010**, *245*(3), 370-377.
http://dx.doi.org/10.1016/j.taap.2010.04.008 PMID: 20406654

[14]   Lord, G.A.; Lim, C.K.; Warnakulasuriya, S.; Peters, T.J. Chemical and analytical aspects of areca nut. *Addict. Biol.,* **2002**, *7*(1), 99-102.
http://dx.doi.org/10.1080/13556210120091455 PMID: 11900628

[15]   Tung, T.H.; Chiu, Y.H.; Chen, L.S.; Wu, H.M.; Boucher, B.J.; Chen, T.H. Keelung Community-based integrated screening pro-gramme No. 2. A population-based study of the association be-tween areca nut chewing and type 2 diabetes mellitus in men (Keelung community-based integrated screening programme No. 2). *Diabetologia,* **2004**, *47*(10), 1776-1781.
http://dx.doi.org/10.1007/s00125-004-1532-2 PMID: 15517150

[16]   Chung, F.M.; Chang, D.M.; Chen, M.P.; Tsai, J.C.; Yang, Y.H.; Shieh, T.Y.; Shin, S.J.; Chen, T.H.; Tai, T.Y.; Lee, Y.J. Areca nut chewing is associated with metabolic syndrome: role of tumor ne-crosis factor-alpha, leptin, and white blood cell count in betel nut chewing-related metabolic derangements. *Diabetes Care,* **2006**, *29*(7), 1714.
http://dx.doi.org/10.2337/dc06-0628 PMID: 16801615

[17]   Guo, S.E.; Huang, T.J.; Huang, J.C.; Lin, M.S.; Hong, R.M.; Chang, C.H.; Chen, M.Y. Alcohol, betel-nut and cigarette con-sumption are negatively associated with health promoting be-haviors in Taiwan: a cross-sectional study. *BMC Public Health,* **2013**, *13*, 257.
http://dx.doi.org/10.1186/1471-2458-13-257 PMID: 23517549

[18]   Tsai, K.Z.; Lin, J.W.; Lin, F.; Su, F.Y.; Li, Y.H.; Lin, Y.P.; Lin, Y.K.; Han, C.L.; Hsieh, C.B.; Lin, G.M. Association of betel nut chewing with exercise performance in a military male cohort: the CHIEF study. *J. R. Army Med. Corps,* **2018**, *164*(6), 399-404.
http://dx.doi.org/10.1136/jramc-2017-000899 PMID: 30012664

[19]   Shafique, K.; Zafar, M.; Ahmed, Z.; Khan, N.A.; Mughal, M.A.; Imtiaz, F. Areca nut chewing and metabolic syndrome: evidence of a harmful relationship. *Nutr. J.,* **2013**, *12*, 67.
http://dx.doi.org/10.1186/1475-2891-12-67 PMID: 23688186

[20]   Verdecchia, P.; Schillaci, G.; Borgioni, C.; Ciucci, A.; Zampi, I.; Battistelli, M.; Gattobigio, R.; Sacchi, N.; Porcellati, C. Cigarette smoking, ambulatory blood pressure and cardiac hypertrophy in es-sential hypertension. *J. Hypertens.,* **1995**, *13*(10), 1209-1215.
http://dx.doi.org/10.1097/00004872-199510000-00016   PMID: 8586813

[21]   Axelsen, M.; Eliasson, B.; Joheim, E.; Lenner, R.A.; Taskinen, M.R.; Smith, U. Lipid intolerance in smokers. *J. Intern. Med.,* **1995**, *237*(5), 449-455.
http://dx.doi.org/10.1111/j.1365-2796.1995.tb00869.x   PMID: 7738484

[22]   Frati, A.C.; Iniestra, F.; Ariza, C.R. Acute effect of cigarette smok-ing on glucose tolerance and other cardiovascular risk factors. *Dia-betes Care,* **1996**, *19*(2), 112-118.
http://dx.doi.org/10.2337/diacare.19.2.112 PMID: 8718429

[23]   Su, F.Y.; Wang, S.H.; Lu, H.H.; Lin, G.M. Association of tobacco smoking with physical fitness of military males in taiwan: The CHIEF study. *Can. Respir. J.,* **2020**, *2020*, 5968189.
http://dx.doi.org/10.1155/2020/5968189 PMID: 31998426

[24]   Mizuno, O.; Okamoto, K.; Sawada, M.; Mimura, M.; Watanabe, T.; Morishita, T. Obesity and smoking: relationship with waist cir-cumference and obesity-related disorders in men undergoing a health screening. *J. Atheroscler. Thromb.,* **2005**, *12*(4), 199-204.
http://dx.doi.org/10.5551/jat.12.199 PMID: 16141623

[25]   Fuchs, F.D.; Chambless, L.E.; Whelton, P.K.; Nieto, F.J.; Heiss, G. Alcohol consumption and the incidence of hypertension: The atherosclerosis risk in communities study. *Hypertension,* **2001**, *37*(5), 1242-1250.
http://dx.doi.org/10.1161/01.HYP.37.5.1242 PMID: 11358935

[26]   Mukamal, K.J.; Rimm, E.B. Alcohol's effects on the risk for coro-nary heart disease. *Alcohol Res. Health,* **2001**, *25*(4), 255-261.
PMID: 11910702

[27]   Albert, M.A.; Glynn, R.J.; Ridker, P.M. Alcohol consumption and plasma concentration of C-reactive protein. *Circulation,* **2003**, *107*(3), 443-447.
http://dx.doi.org/10.1161/01.CIR.0000045669.16499.EC PMID: 12551869

[28]   Chen, K.W.; Meng, F.C.; Shih, Y.L.; Su, F.Y.; Lin, Y.P.; Lin, F.; Lin, J.W.; Chang, W.K.; Lee, C.J.; Li, Y.H.; Hsieh, C.B.; Lin, G.M. Sex-specific association between metabolic abnormalities and elevated alanine aminotransferase levels in a military cohort: The CHIEF study. *Int. J. Environ. Res. Public Health,* **2018**, *15*(3), E545.
http://dx.doi.org/10.3390/ijerph15030545 PMID: 29562671

[29]   Lin, G.M.; Li, Y.H.; Lee, C.J.; Shiang, J.C.; Lin, K.H.; Chen, K.W.; Chen, Y.J.; Wu, C.F.; Lin, B.S.; Yu, Y.S.; Lin, F.; Su, F.Y.; Wang, C.H. Rationale and design of the cardiorespiratory fitness and hospitalization events in armed forces study in Eastern Tai-

wan. *World J. Cardiol.,* **2016**, *8*(8), 464-471.
http://dx.doi.org/10.4330/wjc.v8.i8.464 PMID: 27621774

[30]   Lin, J.W.; Tsai, K.Z.; Chen, K.W.; Su, F.Y.; Li, Y.H.; Lin, Y.P.; Han, C.L.; Lin, F.; Lin, Y.K.; Hsieh, C.B.; Lin, G.M. Sex-specific association between serum uric acid and elevated alanine amino-transferase in a military cohort: The CHIEF study. *Endocr. Metab. Immune Disord. Drug Targets,* **2019**, *19*(3), 333-340.
http://dx.doi.org/10.2174/1871530319666181129163802   PMID: 30499423

[31]   Lin, G.M.; Liu, K. An electrocardiographic system With anthropo-metrics via machine learning to screen left ventricular hypertro-phy among young adults. *IEEE J. Transl. Eng. Health Med.,* **2020**, *8*, 1800111.
http://dx.doi.org/10.1109/JTEHM.2020.2990073   PMID: 32419990

[32]   Chen, Y.J.; Chen, K.W.; Shih, Y.L.; Su, F.Y.; Lin, Y.P.; Meng, F.C.; Lin, F.; Yu, Y.S.; Han, C.L.; Wang, C.H.; Lin, J.W.; Hsieh, T.Y.; Li, Y.H.; Lin, G.M. Chronic hepatitis B, nonalcoholic steato-hepatitis and physical fitness of military males: CHIEF study.

World J. Gastroenterol., **2017**, *23*(25), 4587-4594.
http://dx.doi.org/10.3748/wjg.v23.i25.4587 PMID: 28740347

[33]   Chao, W.H.; Su, F.Y.; Lin, F.; Yu, Y.S.; Lin, G.M. Association of electrocardiographic left and right ventricular hypertrophy with physical fitness of military males: the CHIEF study. *Eur. J. Sport Sci.,* **2019**, *19*(9), 1214-1220.
http://dx.doi.org/10.1080/17461391.2019.1595741   PMID: 30955480

[34]   Huang, P.L. A comprehensive definition for metabolic syndrome. *Dis. Model. Mech.,* **2009**, *2*(5-6), 231-237.
http://dx.doi.org/10.1242/dmm.001180 PMID: 19407331

[35]   Saravanan, R.; Pugalendi, K.V. Effect of piper betel on blood glu-cose and lipid profiles in rats after chronic ethanol administration. *Pharm. Biol.,* **2004**, *42*, 323-327.
http://dx.doi.org/10.1080/13880200490511927

[36]   Zhang, A.; Yao, Y.; Xue, Z.; Guo, X.; Dou, J.; Lv, Y.; Shen, L.; Yu, Y.; Jin, L. A study on the factors influencing triglyceride lev-els among adults in northeast China. *Sci. Rep.,* **2018**, *8*(1), 6388.
http://dx.doi.org/10.1038/s41598-018-24230-4 PMID: 29686322