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The Effect of Metabolic Syndrome on Incidence of Oral Potentially Malignant Disorder

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Abstract

Objectives We aimed to assess the effect of Metabolic Syndrome (MetS) on incident Oral Potentially Malignant Disorder (OPMD).

Design We conducted a prospective cohort study by retrieving data from Changhua community-based integrated screening program (CHCIS) and nationwide oral cancer screening program during the period from 2005 to 2014.

Setting Changhua community-based integrated screening program (CHCIS), Taiwan.

Participants We enrolled 17,638 participants aged over 30 years old.

Main outcomes and measures We measured impact of MetS on an interested outcome of incident OPMD.

Results: The incidence of OPMD among MetS and MetS-free were 8.15 ‰ and 5.66 ‰, respectively. After adjusted for confounders, subjects with MetS showed statistically the elevated risk of being OPMD as compared with those who were free of MetS by 32% (aRR=1.32, 95%CI: 1.14-1.53). The effect remained in the components of MetS, however only for central obesity (aRR=1.24, 95%CI: 1.06-1.45), hyper-triglyceride (aRR=1.27, 95%CI: 1.08-1.49), and hyperglycemia (aRR=1.23, 95%CI: 1.06-1.44). Individual components included central obesity and hyper-triglyceride were also associated with a sub-type of OPMD, leukoplakia.

Conclusion: The temporal influence of MetS on the risk of incident OPMD was noted in our longitudinal cohort study. Therefore, promoting MetS prevention and control program might reduce the occurrence of OPMD and oral cancer.

Strengths and limitations of this study

- A large population-based prospective cohort study was designed to examine the impact of metabolic syndrome (MetS) on incident oral potentially malignant disorder (OPMD).
- This is the first study to investigate the effect of metabolic syndrome on incidence of OPMD as well as sub-type of OPMD, especially leukoplakia and oral submucous fibrosis.
- Investigating other subtypes of OPMD are limited, due to scanty of other OPMD cases in our population.
- The results of our study were summarized from Taiwanese aged over 30, so that external generalization of our results to other regions would be limited especially on ethic, genetic and dietary background.

Introduction

Oral potentially malignant disorders (OPMD) is an disorder that has potential for later progress to oral cancer [1]. Thus, knowledge of the risk factors for an occurrence of OPMD is an important issue for primary prevention of oral cancer [2]. The evidences on tobacco use, betel quid chewing, and alcohol have been well documented as major risk factors for oral potentially malignant disorders (OPMD) [3-7]. Metabolic syndrome (MetS) has been reported to be associated with increased risk of several cancers, including oral cancer [8,9]. In addition to that the presence of MetS has been noted to be associated with OPMD [10,11]. Such association due to the common share of underlying pathways (such as chronic inflammation) could be postulated to be attributed to OPMD. Several studies have proposed the possible biological linkage between OPMD and MetS, which may have pro-inflammatory markers and insulin resistance in common [12-19]. However, the true biological causes accounting for such an association between MetS and OPMD are still elusive. In spite of this, it is still very worthwhile to study how MetS is associated with OPMD by clarification of temporal relationship between MetS and OPMD. A prospective cohort study is therefore required.

In the community-based integrated screening in Changhua, a routine health check-up that embraces biomarker tests for MetS has been conducted annually since 2005 [20] and also the early detection of OPMD and oral cancer has been provided under the instruction of nationwide oral cancer screening program [21]. This screened cohort provides an opportunity to elucidate the effect of MetS on the incidence of OPMD with a normal cohort at baseline following over time until 2014.

Using empirical data from a large population-based integrated screening program in combination with oral cancer screening with oral visual inspection as conducted in Taiwanese

nationwide screening programs, the major aim of this study was to assess temporal influence of MetS on OPMD.

Materials and methods

Study design

Our study design consists of two main steps, the first step is for prevalence (cross-sectional design), and the second step is a longitudinal follow-up for incident cases of OPMD (Figure 1). We conducted cross-sectional analysis to determine the prevalence of OPMD among MetS and MetS-free group at baseline (first screening round). This would allow us to create normal cohorts by excluding those who has been diagnosed as OPMD at first screen and also participants who diagnosed as oral cancer. These cohorts retained to undergo repeated screening.

To address our initial hypothesis that whether MetS plays a role as etiology for OPMD, the prospective long-term follow-up study was adopted. We followed up the OPMD-free cohort who attended subsequence screening and linked the CHCIS and nationwide oral cancer registry iteratively to retrieve the status of OPMD in each screening round. Notably, due to the unmatched time of CHCIS and nationwide screening program, we therefore defined the status of being MetS of participants by using the first screening in CHCIS and also the subtype of OPMD at the first diagnosed outcome of the nationwide screening program.

Study population and data collection

Changhua community-based Integrated Screening is a population based screening program that is identical to the KCIS program which provided multiple cancers screening (liver cancer, breast cancer, colorectal cancer, oral cancer, and cervical cancer), chronic diseases (hyperlipidemia, hypertension, and hyperglycemia) and also MetS and anthropometric measurement [20]. The population in this study consists of dwellers aged 18 years or older that have been invited to participate in oral cancer screening service in Changhua (the CHCIS program) from 2005 to 2014. However, we recruited only participants aged 30 years or older because of sparse numbers of participant lower than 30 years. Therefore, the screening population contained of residents aged over 30 years-old who were free of oral cancer and had been screened at first round and subsequently repeated screening round.

The anthropometric measures for body height, body weight, and circumferences of waist and hip were measured by either public health nurses or well-trained volunteer social workers in the community settings. All participants in the CHCIS program were interviewed to obtain information on education level, oral habits (including betel nut chewing, cigarette smoking, and alcohol drinking), dietary habits, personal disease history, and family disease history, etc. For oral habits, we classified the habit as ex-, ever-, current betel nut chewing, cigarette smoking, or alcohol drinking. In addition to that information which based on questionnaire, the CHCIS program also documented the information of MetS's components, comprised of waist circumference, weight, height, blood pressure and other biochemistry indicator such as fasting glucose, triglyceride and high-density lipoprotein cholesterol levels. Full description of KCIS program [22] and additional information of CHCIS have been described elsewhere [20]. This study was approved by the Institutional Review Board of Taipei Medical University (TMU-JIRB: N201611014)

Patient and Public Involvement

Our study was recruited subjects through the screening programme in Changhua where patient and public involvement was accomplished. In the programme, the Changhua personnel in the local and County Public Health Bureau were responsible. In addition, the staffs also help preparing and advising to facilitate screening service in the community.

The results of our study will be disseminated to the public in community through the personnel of the Changhua County Public Health Bureau.

OPMD detection

Since 2005, the oral visual inspection for all eligible participants has been performed in Changhua County. In each on-site screening center, trained dentists or physicians examined all participants, for those who were clinically diagnosed with oral leukoplakia, erythroleukoplakia, erythroplakia, oral submucous fibrosis (OSF), verrucous hyperplasia and epithelial dysplasia were recorded as positive for OPMD. Instruction on informed consent was first given and approved by those who expressed the willingness of participating in the study.

Metabolic syndrome

Metabolic syndrome (MetS) was defined according to the Epidemiology Task Force Consensus Group criteria (2005) [23] in which participants presented at least three or more of the five components including: (1) central obesity (waist circumference ⩾80 cm for female, and ⩾90 cm for male), (2) hyper-triglyceride (⩾150 mg/dl), (3) low level of high-density lipoprotein cholesterol (HDL-C) (<50 mg/dl for female and <40 mg/dl for male), (4) elevated blood pressure (systolic blood pressure ⩾130 mm Hg or diastolic blood pressure ⩾85 mm Hg), and (5) hyperglycemia (fasting glucose ⩾100 mg/dl).

Statistical analysis

Prevalence of OPMD is presented as cases per 100 persons. Incidence rate of OPMD is presented as cases per 1,000 persons. The univariate Poisson regression model was first used to estimate the rate ratio (RR) for MetS and factors in association with the risk for developing OPMD. The adjusted incidence rate ratio (aRR) was further estimated using the multi-variable Poisson regression model when significant confounding factors from univariate analysis and other factors reported of having significant association with OPMD in previous studies were retained in the model. In addition to the dichotomous variable for whether having MetS or not, we also examined the effect of each individual component of MetS and also MetS's score in separate models with both univariate and multivariate analyses. The magnitude of the effect between MetS and OSF, leukoplakia, and combined erythroleukoplakia, erythroplakia, verrucous hyperplasia and epithelial dysplasia in each separate multi-variable Poisson regression was quantified. Except for the process of selecting variables to be included in the multivariate analysis, statistical significance was set when $p<0.05$. All analyses were conducted with SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

A total of 35,424 subjects aged 30-years or older were included in this study from 2005 to 2014 in Changhua. The prevalence of OPMD was 0.906%. The prevalence of MetS was 31% (Figure 1). Subjects with MetS were statistically significantly 1.46-fold (95% CI: 1.16-1.83) risk for OPMD compared with those without MetS (see Supplementary Table 1).

The incidence of OPMD is shown to vary by demographic and life style factors (Table 1). Most of them were males with median age of 55 years. The incidence of OPMD in subjects with MetS is higher than who are free of MetS, with the corresponding value of 8.15 and 5.66 per thousand person-years respectively.

Table 2 shows the association between MetS and OPMD in the direction that MetS is a cause of OPMD. In univariate analysis, participants with MetS have a 44% increased risk of developing OPMD as compared with those who are MetS-free (RR=1.44, 95%CI: 1.24-1.66). Other factors also showed increased risk of developing OPMD, including male, age less than 70, ever betel nut chewing, cigarette smoking, alcohol drinking, and lower education level. In multivariable analysis, after adjusted for potential confounding factors including age, sex, education level, betel nut chewing, cigarette smoking and alcohol drinking, the MetS remained significant elevated risk of OPMD (aRR=1.32, 95%CI: 1.14-1.53).

In addition to focusing just only defining MetS outcome, we also investigated the individual effect of its components (Table 3). The results showed that central obesity (aRR=1.24, 95%CI: 1.06-1.45), hyper-triglyceride (aRR=1.27, 95%CI: 1.08-1.49) and hyperglycemia (aRR=1.23, 95%CI: 1.05-1.44) had statistically significant increased risk of OPMD. However, the effects of MetS's components were shown differently in Table 4, when investigated in different subtypes of OPMD (leukoplakia and oral submucous fibrosis). For leukoplakia, there were only central obesity (aRR=1.30, 95%CI: 1.08-1.58) and hyper-triglyceride (aRR=1.29, 95%CI: 1.06-1.56) that remained effective significantly, while only hyperglycemia (aRR=1.41, 95%CI: 0.98-1.24) showed a borderline association with increased risk for OSF.

Discussions

In contrast to previous studies that put emphasis on the association between the MetS and OPMD, the main objective of the present study, in addition to corroborating the association studies, was to investigate a temporal sequence pertaining to the effect of MetS on incident OPMD among non-OPMD subjects based on a longitudinal cohort study. It is very interesting to see the statistically significant impact of MetS on incident OPMD was noted. We use the longitudinal follow-up study design to cope with the limit of cross-sectional study design that cannot elucidate the temporal relationship between MetS and OPMD.

The association between MetS and OPMD has been elucidated in several previous cross-sectional studies, conducted in Keelung community-based integrated screening program (KCIS) and in Yunlin county, that MetS was found to elevate the risk of OPMD by 68% and 39%, respectively [10,11] and also confirmed in our current study. We also found that MetS has a 46% increased risk associated with MetS for the presence of OPM.

Our result further indicated that MetS was associated with the risk of incident OPMD. The impact of MetS on OPMD is favored by an estimation of incidence rate ratio with adjustment for confounding factors (aRR=1.32, 95%CI: 1.14-1.53). Moreover, we found three individual components (central obesity, aRR=1.24, 95%CI: 1.06-1.45; hyper-triglyceride, aRR=1.27, 95%CI: 1.08-1.49 and hyperglycemia, aRR=1.23, 95%CI: 1.05-1.44) were statistically significant increasing the risk of OPMD. Such a causal relationship between MetS and the risk for OPM are independent of two well-established risk factors for oral pre-malignant lesions [3], [4], [5] tobacco use and betel quid chewing. Applying such information to oral cancer screening would add the extra value to identify high-risk category of OPMD.

Regarding an independent contributory cause of MetS accounting for OPMD, the link between MetS and tumor progression in OPM and oral cancer might be attributable to the common underlying mechanism, an inflammatory process or immune response for both outcomes. To our knowledge, the exact pathway linking metabolic syndrome and OPMD is still not clear; however, previous studies proposed common sharable mechanism between MetS and OPMD, consisted of pro-inflammatory markers (TNF-alpha and C-reactive protein, IL-6), and insulin resistance [12,19,24]. MetS affects cancer tumor cells through an increasing proliferation, angiogenesis and damage to the DNA molecule under chronic hyperglycemia, insulin resistance and hyperinsulinemia [25-29]. In addition, MetS particularly with insulin resistance can overstimulate insulin growth factor-1 (IGF-1) and insulin receptor. An increasing and changing of IGF-1 signaling pathway and insulin receptor expression might lead to increase the risk of cancer [30]. In present study, we found that central obesity, hyperglycemia and hypertriglyceridemia are significant individual components of MetS for development of OPMD. Previous study revealed that the central obesity can stimulate insulin resistance, dyslipidemia and systematic inflammation and in turn, the components considered to play vital role in pathogenesis of certain type of cancer [31,32]. Moreover, the insulin resistance is also associated with an increasing of the production of glucose and triglyceride, both were highly associated with the risk of developing OPMD in our analysis.

We also estimated the effect of MetS on subtypes of OPMD (leukoplakia and OSF), and found that MetS increased risk of two types of OPMD, leukoplakia and OSF; however, statistically significance was only found in leukoplakia. In addition, among MetS's components, only central obesity and hyper-triglyceride significantly elevated risk of leukoplakia. These results were inconsistent with previous study that found only hyper-triglyceride and

hyperglycemia significantly increased risk of leukoplakia [11]. Considering of hyper-triglyceride in leukoplakia, previous study reported significantly higher triglyceride level in leukoplakia than healthy people [33]. An increasing triglyceride is possibly due to the excessive release of free fatty acids, which resulted from insulin resistance. Moreover, insulin resistance can be stimulated by central obesity. In addition, Meisel et al, reported that visceral obesity was more likely to find in people with leukoplakia than those of non-leukoplakia [34]. The aforementioned studies support our findings that two of MetS's components, central obesity and hyper-triglyceride, associated with leukoplakia. However, the mechanism to explain this is still lacking.

Even though our study demonstrated that hyperglycemia didn't significantly increase the risk of OSF, the aRR showed largest increased risk magnitude in OSF. Regarding OSF, it has been recognized that the development of fibrosis is the pathologically responsible for tissue injury in which caused by chronic hyperglycemia. The development of fibrosis was driven by accumulation of extracellular matrix (ECM) [35].

One of the unique characteristics of OSF is the symptom of mouth opening restriction [36], [37,38]. A possible causation for restricted mouth opening might be because of dynamics of ECM deposited around muscle fibers in different stages of OSF, and these lead to the consequence of loss of variety of ECM molecules including elastin into the uniform of collagen type I replacing muscle fibers [39]. Notably, it has been shown that hyperglycemia can alter the collagenolysis [40] and also ECM's components interaction through advanced glycation end products (AGEs) modification [41-45]. These reasons mentioned above may support the borderline impact of hyperglycemia on OSF and its symptom.

Another possibility of the discordance between these findings might be due to the difference of study approaches and community which dietary differs from each other. However,

both studies pointed out that the hyper-triglyceride and hyperglycemia were related to OPMD. Exceptionally to those biological aspects, these results are supported by strong epidemiological study design in which we followed up the study population from being either MetS or OPMD-free until occurrence of interested outcomes (OPMD for MetS-free cohort and MetS for OPMD-free cohort).

In the view of oral cancer control, primary prevention is aimed to reduce the exposure to risk factors. In Taiwan, several cessation campaigns have been launched but most of these efforts were considered just for conventional risk factors including cigarette smoking and betel nut chewing. Our study result showed that MetS is one of risk factor for OPMD. In addition, a recent study also revealed that sweet beverage consumption elevated risk of overall cancer and breast cancer [46]. Promoting MetS prevention program with controlling of sugar-sweetened beverage or diet might reduce OPMD and oral cancer incidence in the future. Moreover, in countries like Taiwan that has nationwide oral cancer screening program, we recommended to consider MetS as a criterion for screening of oral cancer in addition to age and conventional risk factors.

Several limitations existed in our study. First, several confounding factors that may link MetS and oral cancer, such as family history of oral cancer and history of chronic diseases other than MetS, were not considered. Second, the results of our study were summarized from Taiwanese aged over 30, so that external generalization of our results to other regions would be limited especially on ethic genetic and dietary background. Third, we analyzed only subtype of OPMD including only leukoplakia and OSF, due to scanty of other OPMD cases in our population. Lastly, we did not estimate the effect of OPMD on MetS, for there were not enough incident MetS cases from people who diagnosed as OPMD at baseline.

In conclusion, our prospective cohort study design affirmed the direction that MetS elevated risk of OPMD. This epidemiological evidence would lead new insight for policy makers to promote MetS prevention in order to reduce OPMD and oral cancer in the future.

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Contributors: PS, ST-W, YP-Y, and AMF-Y conceived conceptualization, and methodology. SM-P and YP-Y contributed to data curation, investigation. PS, SSL-C, and AMF-Y carried out statistical analysis. PS and ST-W wrote original draft. This study was supervised by YP-Y and AMF-Y. HH-C and PS* participated in editing manuscript. All authors have reviewed and approved the final manuscript

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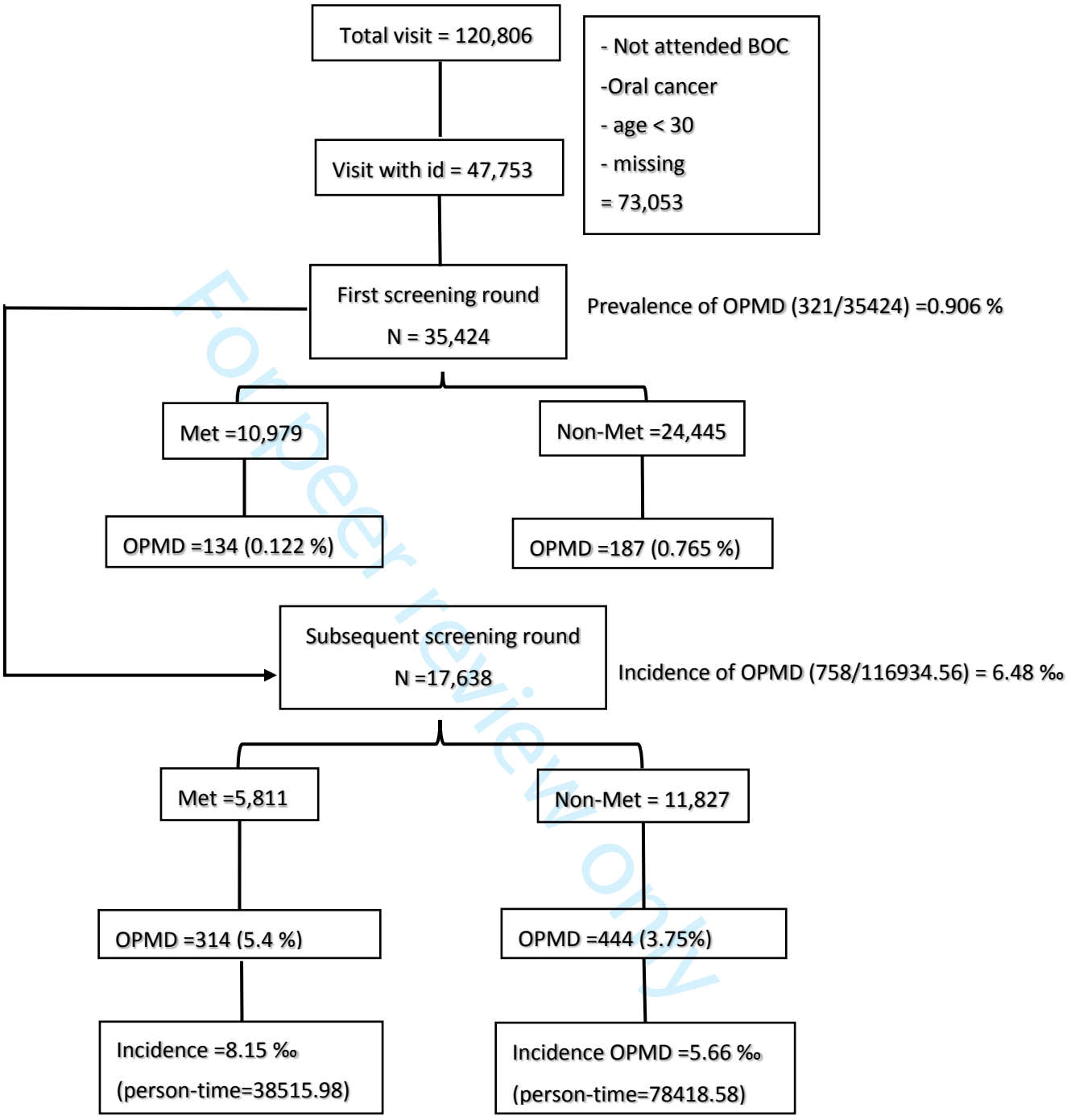

Figure 1 The flow chart for prospective normal cohort study design

Table 1 The incidence (per 1,000) of oral potentially malignant disorders by demographic features, status of metabolic syndrome and other associated risk factors

	Person- years	OPMD		OSF		Leukoplakia		Erykoplakia + Erythroleukoplakia + Verrucous hyperplasia + Epithelial Dysplasia	
		No.	Incidence, ‰	No.	Incidence, ‰	No.	Incidence, ‰	No.	Incidence, ‰
Overall	116934.6	758	6.5	150	1.3	521	4.5	87	0.7
Metabolic syndrome									
Yes	38516.0	314	8.2	58	1.5	219	5.7	37	1.0
No	78418.6	444	5.7	92	1.2	302	3.9	50	0.6
Age									
30-39	8321.2	52	6.2	13	1.6	28	3.4	11	1.3
40-49	29240.6	218	7.5	42	1.4	154	5.3	22	0.8
50-59	35218.4	287	8.1	49	1.4	205	5.8	33	0.9
60-69	27820.5	167	6.0	37	1.3	115	4.1	15	0.5
70+	16333.9	34	2.1	9	0.6	19	1.2	6	0.4
Gender									
Male	104766.8	744	7.1	147	1.4	511	4.9	86	0.8
Female	12167.8	14	1.2	3	0.2	10	0.8	1	0.1
Betel nut chewing									
Never	79041.1	265	3.4	39	0.5	203	2.6	23	0.3
Quit	23802.4	252	10.6	62	2.6	162	6.8	28	1.2
Current	14005.4	241	17.2	49	3.5	156	11.1	36	2.6
Cigarette									

smoking									
Never	46288.0	104	2.2	22	0.5	75	1.6	7	0.2
Quit	24719.2	133	5.4	36	1.5	82	3.3	15	0.6
Current	45841.5	521	11.4	92	2.0	364	7.9	65	1.4
Alcohol drinking									
Never	53551.6	224	4.2	48	0.9	155	2.9	21	0.4
Quit	6825.2	63	9.2	10	1.5	44	6.4	9	1.3
Current	56474.9	471	8.3	92	1.6	322	5.7	57	1.0
Education level									
University	13701.3	55	4.0	4	0.3	47	3.4	4	0.3
Senior high school	26862.0	182	6.8	39	1.5	126	4.7	17	0.6
Junior high school or lower	76022.5	519	6.8	107	1.4	347	4.6	65	0.9

OSF: oral submucous fibrosis

Table 2 The association between MetS, other factors and oral potentially malignant disorders (MetS → OPMD)

	RR	95%CI		aRR	95%CI	
Metabolic syndrome						
Yes vs No	1.44	1.24	1.66	1.32	1.14	1.53
Gender						
Male vs Female	6.90	3.90	12.20	3.34	1.86	6.00
Age groups (vs 70+)						
30-39	3.00	1.95	4.62	2.53	1.62	3.95
40-49	3.45	2.40	4.95	2.66	1.83	3.85
50-59	3.64	2.55	5.20	3.13	2.19	4.48
60-69	2.80	1.93	4.04	2.53	1.75	3.66
Betel nut chewing (vs Never)						
Quit	3.11	2.61	3.71	2.07	1.69	2.54
Current	5.11	4.29	6.10	2.81	2.29	3.46
Cigarette smoking (vs Never)						
Quit	2.40	1.85	3.12	1.37	1.01	1.85
Current	5.09	4.10	6.31	2.65	2.06	3.42
Alcohol drinking (vs Never)						
Quit	1.94	1.65	2.28	1.21	0.90	1.64
Current	2.20	1.65	2.91	1.01	0.85	1.21
Education level (vs Junior high school or lower)						
Senior high school	0.99	0.83	1.17	0.94	0.78	1.12
University	0.59	0.45	0.78	0.78	0.58	1.05

aRR: adjusted rate ratio; **CI**: confidence interval

Table 3 The effect of metabolic syndrome components on oral potentially malignant disorders

	All OPMD			
	aRR*	**95%CI**		**p-value**
Component of metabolic syndrome				
Central obesity	1.24	1.06	1.45	0.0066
Hyper-triglyceride	1.27	1.08	1.49	0.0033
Low HDL-C	1.10	0.94	1.29	0.2512
Elevated blood pressure	0.90	0.77	1.05	0.1637
Hyperglycemia	1.23	1.05	1.44	0.0096
Metabolic syndrome score	1.14	1.08	1.20	<.0001

aRR: adjusted rate ratio; **CI**: confidence interval.

* adjusted incidence rate ratio for components of metabolic syndrome and metabolic syndrome score were treated in different models with simultaneously adjusted all other confounders including age, gender, education level, betel nut chewing, cigarette smoking and alcohol drinking.

Table 4 The association between metabolic syndrome and sub-types of oral potentially malignant disorders using multi-variable Poisson regression

	Leukoplakia				OSF			
	aRR*	95%CI		p-value	aRR*	95%CI		p-value
Metabolic syndrome								
Yes vs No	1.36	1.14	1.62	0.0007	1.22	0.87	1.71	0.2572
Component of metabolic syndrome								
Central obesity	1.30	1.08	1.58	0.0059	1.06	0.74	1.52	0.7467
Hyper-triglyceride	1.29	1.06	1.56	0.0108	1.20	0.83	1.75	0.3390
Low HDL-C	1.17	0.97	1.42	0.1083	0.95	0.65	1.38	0.7756
Elevated blood pressure	0.90	0.74	1.08	0.2472	0.95	0.66	1.37	0.7949
Hyperglycemia	1.18	0.98	1.43	0.0848	1.41	0.98	2.03	0.0627
Metabolic syndrome score	1.16	1.09	1.24	<.0001	1.10	0.98	1.24	0.0963

aRR: adjusted rate ratio; **CI**: confidence interval; **OSF**: oral submucous fibrosis

* adjusted incidence rate ratio for metabolic syndrome, components of metabolic syndrome, and metabolic syndrome score were treated in different models with all other confounders adjusted simultaneously including age, gender, education level, betel nut chewing, cigarette smoking and alcohol drinking

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Supplement table 1 The association between MetS, other factors and prevalence of oral potentially malignant disorders

	OR	95%CI		aOR	95%CI	
Metabolic syndrome						
Yes vs No	1.60	1.28	2.00	1.46	1.16	1.83
gender						
M vs F	7.65	4.87	12.04	2.71	1.64	4.48
Age groups (vs 70+)						
30-39	0.83	0.39	1.77	0.86	0.39	1.90
40-49	1.78	1.09	2.92	1.41	0.84	2.37
50-59	2.69	1.68	4.29	2.40	1.48	3.88
60-69	1.83	1.11	3.01	1.76	1.07	2.92
Betel nut chewing (vs Never)						
Quit	3.51	2.69	4.57	2.48	1.62	3.79
Current	5.69	4.34	7.47	4.65	3.23	6.68
Cigarette smoking (vs Never)						
Quit	4.61	3.17	6.70	2.40	1.85	3.12
Current	8.96	6.58	12.21	5.09	4.10	6.31
Alcohol drinking (vs Never)						
Quit	2.83	1.78	4.48	1.04	0.64	1.68
Current	2.56	2.02	3.25	1.04	0.80	1.35
Education level (vs Junior high school or lower)						
Senior high school	1.03	0.80	1.33	1.10	0.84	1.44
University	0.57	0.38	0.85	0.87	0.57	1.31

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Pages
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7,8
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7,9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	10 (Figure)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted	10,11

		estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12,15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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The Effect of Metabolic Syndrome on Incidence of Oral Potentially Malignant Disorder: A Prospective Cohort Study

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Abstract

Objectives We aimed to assess the effect of metabolic syndrome (MetS) on incident oral potentially malignant disorder (OPMD).

Design We conducted a prospective cohort study from Changhua community-based integrated screening (CHCIS) program and nationwide oral cancer screening program during the period between 2005 and 2014.

Setting Changhua community-based integrated screening CHCIS, Taiwan.

Participants We enrolled 17,590 participants aged over 30 years old.

Main outcomes and measures We assessed the impact of MetS on the outcome measured by incident OPMD.

Results: The incidence of OPMD among subjects with and without MetS were 7.68 ‰ and 5.38 ‰, respectively. After adjusting for confounders, subjects with MetS showed a statistically greater risk of developing OPMD than those who were free of MetS by 33% (aRR=1.33, 95% CI: 1.14-1.55). Individual components of MetS still remained significant, including central obesity (aRR=1.22, 95% CI: 1.04-1.44), hyper-triglyceride (aRR=1.26, 95% CI: 1.07-1.49), and hyperglycemia (aRR=1.20, 95% CI: 1.02-1.41). Central obesity and hyper-triglyceride were also statistically associated with a sub-type of OPMD, leukoplakia.

Conclusion: The temporal influence of MetS on the risk of incident OPMD was noted in our prospective cohort study. Therefore, promoting MetS prevention and control program might reduce the occurrence of OPMD and oral cancer.

Strengths and limitations of this study

- A large population-based prospective cohort study was conducted to examine the impact of metabolic syndrome (MetS) on incident oral potentially malignant disorder (OPMD).
- This is the first study to investigate the effect of metabolic syndrome on incidence of OPMD as well as sub-types of OPMD, especially leukoplakia and oral submucous fibrosis.
- Investigating other subtypes of OPMD are limited, due to sparse other OPMD cases in our population.
- The results of our study are summarized from Taiwanese aged over 30 so that external generalization of our results to other regions would be limited especially on ethnic, genetic and dietary background.

Introduction

Oral potentially malignant disorder (OPMD) is an disorder that has potential for subsequent progression to oral cancer [1]. Thus, to have a better understanding of risk factors accounting for the occurrence of OPMD is an important issue for primary prevention of oral cancer [2]. Evidence on tobacco use, betel quid chewing, and alcohol drinking has been well documented as major risk factors for OPMD [3-4]. Metabolic syndrome (MetS) has been reported to be associated with the increased risk of several cancers, including oral cancer [5,6]. MetS has also been noted to be associated with OPMD [7,8]. Such an association due to the common shared underlying pathway (such as chronic inflammation) could be attributed to OPMD. Several studies have proposed the possible biological linkage between OPMD and MetS, which may have pro-inflammatory markers and insulin resistance in common [9-10]. However, the true biological causes accounting for such an association between MetS and OPMD are still elusive. In spite of this, it is still very worthwhile to study how MetS is associated with OPMD by the clarification of temporal relationship between MetS and OPMD. A prospective cohort study is therefore required.

In the Changhua community-based integrated screening (CHCIS), a routine health check-up that embraces biomarker tests for MetS has been conducted annually since 2005 [11]. The early detection of OPMD and oral cancer has been provided under the instruction of nationwide oral cancer screening program [12]. This screened cohort provides an opportunity to elucidate the effect of MetS on the incidence of OPMD with a normal cohort at baseline following over time until 2014.

Using empirical data from a large population-based integrated screening program in combination with nationwide oral cancer screening program with oral visual inspection, the major aim of this study was to assess the temporal influence of MetS on OPMD.

Materials and methods

Study design

Our study design consists of two main steps, the first step is tailored for prevalence (cross-sectional design), and the second step is a longitudinal follow-up for incident cases of OPMD (Figure 1). We conducted cross-sectional analysis to determine the prevalence of OPMD among MetS and MetS-free group at baseline (identified at the first screening round). This would allow us to create a normal cohort by excluding those who has been diagnosed as OPMD or oral cancer before or at first screen. Subjects in this normal cohort have underwent repeated screening continuously.

To address our initial hypothesis that whether MetS plays a role as etiology for OPMD, a prospective follow-up study was adopted. We followed the OPMD-free cohort who attended subsequence screening in the nationwide oral cancer screening program to identify those with OPMD diagnosis in subsequent screening rounds. It should be noted that subjects may attend the CHCIS and nationwide oral cancer screening program at different times. We defined the status of MetS of participants by using the first screen in CHCIS, and the first diagnosis of OPMD in the nationwide oral cancer screening program.

Study population and data collection

CHCIS program is a population-based screening program, which followed the service model of the Keelung community-based integrated screening (KCIS) program [13]. These programs provided screening services of multiple cancers (liver cancer, breast cancer, colorectal cancer, oral cancer, and cervical cancer), chronic diseases (hyperlipidemia, hypertension, and hyperglycemia, and MetS), and anthropometric measurements [11]. The population in this study

consists of dwellers aged 30 years or older that have been participated in both CHCIS and the nationwide oral cancer screening program between 2005 and 2014. Subjects who had a diagnosis of oral cancer before the first attendance to the CHCIS program were excluded.

All participants were instructed to follow an 8-hour fasting before blood drawing. Biochemical examination on fasting glucose and lipid profiles was performed. The anthropometric measures for body height, body weight, and circumferences of waist and hip were measured by either public health nurses or well-trained volunteer social workers in the community settings. All participants in the CHCIS program were interviewed to obtain information on education level, oral habits (including betel nut chewing, cigarette smoking, and alcohol drinking), dietary habits, personal disease history, and family disease history. For oral habits, we classified the habit as never-, quit-, and current use. Quitting in our study refers to that participants who had ever habitual use of chewing betel quid, smoking cigarette, or drinking alcohol; however, at the time of interview, they had no regular consumption of betel quid, cigarette, or alcohol. Dietary factors, including meat, vegetable and fruit consumption were classified as seldom (including never), infrequent, and frequent consumption. Infrequent meat consumption was defined as having 1-2 units per day, and frequent meat consumption as 3-4 units per day. Infrequent vegetable consumption was defined as having a half or 1 bowl per day, and frequent vegetable consumption was defined as 3-4 bowls per day. Infrequent fruit consumption was defined as having 1-4 times per week, and frequent-fruit consumption as more than 5 times per week.

Instruction on informed consent was first given and approved by those who expressed the willingness of participating in the study. This study was approved by the Institutional Review Board of Taipei Medical University (TMU-JIRB: N201611014)

OPMD detection

Since 2005, the oral visual inspection for all eligible participants has been performed in Changhua County. In each on-site screening center, trained dentists or physicians examined all participants. For those who were clinically diagnosed with oral leukoplakia, erythroleukoplakia, erythroplakia, oral submucous fibrosis (OSF), and verrucous hyperplasia were recorded as positive for OPMD.

Metabolic syndrome

Metabolic syndrome (MetS) was defined according to the Epidemiology Task Force Consensus Group criteria (2005) [14] in which participants presented at least three or more of the five components including: (1) central obesity (waist circumference ⩾80 cm for female, and ⩾90 cm for male), (2) hyper-triglyceride (⩾150 mg/dl), (3) low level of high-density lipoprotein cholesterol (HDL-C) (<50 mg/dl for female and <40 mg/dl for male), (4) elevated blood pressure (systolic blood pressure ⩾130 mm Hg or diastolic blood pressure ⩾85 mm Hg), and (5) hyperglycemia (fasting glucose ⩾100 mg/dl).

Patient and Public Involvement

Participants in our study were recruited through the CHCIS programme. Participants did not involve in designing or conducting the study. Staff in the Changhua County Public Health Bureau and local health centers were responsible for preparation and implementation of the screening service in the community.

The results of our study will be disseminated to the public in community through the Changhua County Public Health Bureau.

Statistical analysis

Prevalence of OPMD was presented as cases per 100 persons. Incidence rate of OPMD was presented as cases per 1,000 person-years. The univariate Poisson regression model was first used to estimate the rate ratio (RR) for MetS and factors in association with the risk for developing OPMD. The adjusted rate ratio (aRR) was further estimated using the multi-variable Poisson regression model when significant confounding factors from the univariate analyses and other factors reported of having significant association with OPMD in previous studies were retained in the model. In addition to the dichotomous variable for whether to have MetS or not, we also examined the effect of each individual component of MetS and also MetS's score in separate models with both univariate and multivariate analyses. The magnitude of the effect between MetS and sub-types of OPMD was estimated in separate multi-variable Poisson regression models. Statistical significance was set when $p<0.05$. All analyses were conducted with SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

A total of 35,411 subjects aged 30-years or older were included in this study from 2005 to 2014 in Changhua. The prevalence of OPMD was 0.87% (=306/35,411). The prevalence of MetS was 31% (=10,974/35,411) (Figure 1). Subjects with MetS had a statistically significantly 1.44 times (95% CI: 1.14-1.82) likely to develop the risk for OPMD compared with those without MetS (see Supplementary Table 1).

The incidence of OPMD is shown to vary by demographic and life style factors (Table 1). The incidence of OPMD in subjects with MetS (7.68 per 1000 person-years) was higher than those who were free of MetS (5.38 per 1000 person-years). Male, subjects aged between 40-59 years, higher body mass index (BMI), higher blood pressure, and elevated lip profiles tended to show a higher risk of OPMD compared with their complementary groups. Ever having habit of betel quid chewing, smoking, and alcohol drinking were associated with higher incidence of OPMD. High consumption of meat and lower consumption of vegetables and fruit were also related to higher risk of OPMD.

Table 2 shows the effect of MetS on the risk of OPMD. In the univariate analysis, participants with MetS had a 42% greater risk of developing OPMD than those who were MetS-free (RR=1.42, 95% CI: 1.22-1.66). Other factors also showed increased risks of developing OPMD, including male, age less than 70, betel nut chewing, cigarette smoking, alcohol drinking, meat consumption, and lower education level. In multivariable analysis, after adjusting for potential confounding factors including age, sex, education level, betel nut chewing, cigarette smoking, meat consumption, vegetable consumption, the intake of fruit, and alcohol drinking, MetS leading to the elevated risk of OPMD still remained significant (aRR=1.33, 95% CI: 1.14-1.55).

In addition to focusing only on MetS outcome, we also investigated the effects of individual components of MetS (Table 3). The results showed that central obesity (aRR=1.22, 95% CI: 1.04-1.44), hyper-triglyceride (aRR=1.26, 95% CI: 1.07-1.49) and hyperglycemia (aRR=1.20, 95% CI: 1.02-1.41) led to a statistically significant increased risk of OPMD. However, the effects of MetS's components were different with respect to the subtypes of OPMD (Table 4). For leukoplakia, only central obesity (aRR=1.30, 95% CI: 1.07-1.57) and hyper-triglyceride (aRR=1.29, 95% CI: 1.06-1.57) remained significant. Only hyperglycemia (aRR=1.43, 95% CI: 0.99-2.05) showed a borderline association with an increased risk for OSF. MetS led to an elevated risk of verrucous hyperplasia by 33%, but it was not statistically significant due to the small number (aRR=1.33, 95% CI: 0.51-3.46). Same phenomenon was noted for erythroplakia and erythroleukoplakia (aRR=1.59, 95% CI: 0.67-3.75). We also provide the detailed results on the effects of dichotomous MetS, individual components of MetS and MetS score for all OPMD (Supplementary Tables 2-3), leukoplakia (Supplementary Tables 4-6), OSF (Supplementary Tables 7-9), verrucous hyperplasia (Supplementary Tables 10-12), and erythroplakia and erythroleukoplakia (Supplementary Tables 13-15).

Discussion

In contrast to previous studies that put emphasis on the association between MetS and OPMD, the main objective of the present study, in addition to corroborating the association studies, was to investigate a temporal sequence pertaining to the effect of MetS on incident OPMD based on a longitudinal cohort study. The statistically significant impact of MetS on incident OPMD was observed. We used the longitudinal follow-up study design to cope with the limitation of the cross-sectional study design that cannot elucidate the temporal relationship between MetS and OPMD.

The association between MetS and OPMD has been elucidated in several previous cross-sectional studies, conducted in Keelung community-based integrated screening program (KCIS) and in Yunlin county, in that MetS was found to elevate the risk of OPMD by 68% and 39%, respectively [7,8], which has been also confirmed in our current study. We also found that MetS led to a 44% increased risk associated with MetS for the presence of OPMD.

Furthermore, given a prospective cohort study design, our study further demonstrated the temporal effect of MetS and individual components on incident OPMD. Such a causal relationship between MetS and the risk for OPMD is independent of two well-established risk factors for oral pre-malignant lesions, smoking and betel quid chewing [3], [15], [16]. Applying such information to oral cancer screening would provide additional value for identifying high-risk category of OPMD.

Regarding an independent contributory cause of MetS accounting for OPMD, the link between MetS and tumor progression in OPMD and oral cancer might be attributable to the common underlying mechanism, an inflammatory process or immune response for both outcomes. To our knowledge, the exact pathway linking MetS and OPMD is still unclear.

However, cytokine is often secreted by immune cells in response to inflammation. This would lead to the greater amount of C-Reactive Protein (CRP) [17]. CRP is known as a biomarker for cardiovascular disease. Recently, it was found to increase oxygen radical as well [18]. These inflammatory factors can activate oncogenes and inactivate tumor suppressor genes, and can potentially induce cell proliferation and prolong cell survival, which may result in genetic instability with an increased risk of cancer [19]. Previous studies proposed common shared mechanisms between MetS and OPMD, including pro-inflammatory markers (TNF-alpha and CRP, IL-6), and insulin resistance [9,10,20]. Therefore, MetS may affect cancer tumor cells through an increasing proliferation, angiogenesis and damage to the DNA molecule under chronic hyperglycemia, insulin resistance and hyperinsulinemia [21-22]. In addition, MetS particularly with insulin resistance can overstimulate insulin growth factor-1 (IGF-1) and insulin receptor. An increasing and changing of IGF-1 signaling pathway and insulin receptor expression might lead to an increased risk of cancer as well [17]. In present study, we found that central obesity, hyperglycemia, and hypertriglyceridemia were significant individual components of MetS responsible for the development of OPMD. Previous studies revealed that the central obesity can stimulate insulin resistance, dyslipidemia and systematic inflammation. In turn, the individual components were considered to play a vital role in the pathogenesis of certain type of cancers [23,24]. Moreover, the insulin resistance was also associated with an increase in the production of glucose and triglyceride. Both were highly associated with the risk of developing OPMD in our analysis.

Betel quid's substances (nitrosated and arecal alkaloid derivatives) have been confirmed to increase the risk of oral cancer and OPMD. This effect was not restricted to their direct contact tissue. Lee et al, found that betel quid chewing and components of MetS have a positive

correlation explained by oxidative stress and inflammation [25]. An increase in the risk of oral cancer or OPMD by consuming betel quid and also cigarette smoking or alcohol drinking were noted in our study even those patients who had quitted these habits because they have had exposed to those carcinogenesis components for a sufficient period. Our results were consistent with previous studies, demonstrated that former or ex- consuming of these oral habits still had higher risk of oral cancer, leukoplakia and OSF compared with non-users[26, 27].

Aside from betel quid, foods were also of concern. Numbers of studies unveiled that potential diet such as red meat was associated with increased IL-6 [28], and vegetable and fruit could lowered CRP [29]. In our study, we found that only fruit with high consumption was shown to be a protective factor of OPMD. Our findings were consistent with Fann et al, and Maserejian et al., who found that fruit decreased the risk of periodontal disease and OPMD, respectively [30,31]. Interestingly, fruit could reduce the risk of MetS as well [32]. Therefore, these findings support our hypothesis that inflammatory is one of the potential mechanisms underlying between MetS and OPMD.

We examined the effect of MetS on subtypes of OPMD, and found that MetS was associated with an increased risk of leukoplakia, but not in other sub-types, including OSF, verrucous hyperplasia, and erythleukoplakia due to small number of cases. For leukoplakia, among MetS's components, only central obesity and hyper-triglyceride significantly elevated the risk of leukoplakia. These results were inconsistent with the previous study that found only hyper-triglyceride and hyperglycemia significantly increased risk of leukoplakia [8]. Considering of hyper-triglyceride in leukoplakia, previous study reported significantly higher triglyceride level in leukoplakia than healthy people [33]. An increasing triglyceride was possibly due to the excessive release of free fatty acids, which resulted from insulin resistance. Moreover, insulin

resistance can be stimulated by central obesity. In addition, Meisel et al, reported that visceral obesity was more likely to be found in people with leukoplakia than those of non-leukoplakia [34]. The aforementioned studies support our findings that two of MetS's components, central obesity and hyper-triglyceride, associated with leukoplakia. However, the mechanism to explain this is still unclear.

Even though our study demonstrated that hyperglycemia did not significantly increase the risk of OSF, the aRR showed the largest increased risk magnitude in OSF. Regarding OSF, it has been recognized that the development of fibrosis is the pathologically responsible for tissue injury caused by chronic hyperglycemia. The development of fibrosis was driven by the accumulation of extracellular matrix (ECM) [35].

One of the unique characteristics of OSF is the symptom of mouth opening restriction [36], [37,38]. A possible causation for restricted mouth opening might be because of dynamics of ECM deposited around muscle fibers in different stages of OSF, and these lead to the consequence of loss of variety of ECM molecules including elastin into the uniform of collagen type I replacing muscle fibers [39]. Notably, it has been shown that hyperglycemia can alter the collagenolysis [40] and also ECM's components interaction through advanced glycation end products (AGEs) modification [41-42]. These reasons mentioned above may support the borderline impact of hyperglycemia on OSF and its symptom.

Another possibility of the discordance between these findings might be due to the difference of study approaches and community which dietary habits differed from each other. However, both studies pointed out that the hyper-triglyceride and hyperglycemia were related to OPMD. Exceptionally to those biological aspects, these results are supported by strong

epidemiological study design in which we followed up the study population from being OPMD-free until occurrence of OPMD.

In the view of oral cancer control, primary prevention aims to reduce the exposure to risk factors. In Taiwan, several cessation campaigns have been launched but most of these efforts were considered just for conventional risk factors including cigarette smoking and betel nut chewing. Our study result showed that MetS was one of risk factor for OPMD. In addition, a recent study also revealed that sweet beverage consumption elevated risk of overall cancer and breast cancer [43]. Promoting MetS prevention program after controlling for sugar-sweetened beverage or diet might reduce OPMD and oral cancer incidence in the future.

Several limitations existed in our study. First, several confounding factors that may link MetS and oral cancer, such as family history of oral cancer and history of chronic diseases other than MetS, were not considered. Second, the results of our study were derived from Taiwanese aged over 30, so that external generalization of our results to other regions would be limited especially on ethnic genetic and dietary background. Third, the association between MetS and verrucous hyperplasia, erythroplakia, and erythroleukoplakia should be interpreted with great caution, due to scanty of cases in our population. Fourth, there exits possible information bias for self-reported variables, especially oral habits. Betel nut chewing, smoking, and alcohol drinking are behaviors that are deviant from social norms and regulations, and can be possibly under-reported. Evidence on this phenomena has been shown in reporting smoking behavior [44, 45]. This might explain the 38 subjects of OSF who had reported never betel quid chewing, which contradicts the well-known association between OSF and betel quid chewing.

In conclusion, our prospective cohort study design affirmed the direction that MetS elevated risk of OPMD. This epidemiological evidence would lead new insight for policy makers to promote MetS prevention in order to reduce OPMD and oral cancer in the future.

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Figure Legend

Figure 1 The flow chart for prospective normal cohort study design

Table 1 The incidence (per 1,000) of oral potentially malignant disorders by demographic features, status of metabolic syndrome and other associated risk factors

			OPMD		OSF		leukoplakia		Verrucous hyperplasia		Erykoplakia+ Erythroleukoplakia	
	N	Person years	No.	‰	No.	‰	No.	‰	No.	‰	No.	‰
Overall	17,590	116732.06	716	6.13	149	1.28	521	4.46	20	0.17	26	0.22
Metabolic Syndrome												
Yes	5,789	38416.38	295	7.68	58	1.51	219	5.70	7	0.18	11	0.29
No	11,801	78315.68	421	5.38	91	1.16	302	3.86	13	0.17	15	0.19
Age												
30-39	1,178	8296.07	47	5.67	13	1.57	28	3.38	1	0.12	5	0.60
40-49	4,359	29193.98	210	7.19	42	1.44	154	5.28	8	0.27	6	0.21
50-59	5,538	35137.59	267	7.60	48	1.37	205	5.83	6	0.17	8	0.23
60-69	4,176	27778.33	160	5.76	37	1.33	115	4.14	4	0.14	4	0.14
70+	2,339	16326.09	32	1.96	9	0.55	19	1.16	1	0.06	3	0.18
Sex												
Male	15,619	104569.65	703	6.72	146	1.40	511	4.89	20	0.19	26	0.25
Female	1,971	12162.41	13	1.07	3	0.25	10	0.82	0	0.00	0	0.00
Education												
University	2140	13691.15	53	3.87	4	0.29	47	3.43	1	0.07	1	0.07
Senior high school	4173	26814.93	174	6.49	39	1.45	126	4.70	3	0.11	6	0.22
Junior high school or lower	11228	75877.21	487	6.42	106	1.40	347	4.57	16	0.21	18	0.24
Betel quid chewing												
Never	11,925	79006.46	256	3.24	38	0.48	203	2.57	10	0.13	5	0.06
Quit*	3,544	23719.97	236	9.95	62	2.61	162	6.83	6	0.25	6	0.25
Current	2,110	13920.02	224	16.09	49	3.52	156	11.21	4	0.29	15	1.08
Smoking												
Never	6,976	46286.91	101	2.18	21	0.45	75	1.62	1	0.02	4	0.09
Quit*	3,656	24678.95	126	5.11	36	1.46	82	3.32	3	0.12	5	0.20
Current	6,947	45680.37	489	10.70	92	2.01	364	7.97	16	0.35	17	0.37

Alcohol drinking												
Never	8,041	53484.46	212	3.96	48	0.90	155	2.90	4	0.07	5	0.09
Quit*	1,009	6798.76	58	8.53	10	1.47	44	6.47	2	0.29	2	0.29
Current	8,529	56365.96	446	7.91	91	1.61	322	5.71	14	0.25	19	0.34
BMI (kg/m2)												
<18.5	422	2852.29	9	3.16	5	1.75	3	1.05	0	0.00	1	0.35
18.5-24.9	8,844	58824.11	313	5.32	66	1.12	221	3.76	13	0.22	13	0.22
>25	8,324	55055.66	394	7.16	78	1.42	297	5.39	7	0.13	12	0.22
Triglyceride (mg/dl)												
<150	12,178	81399.38	405	4.98	87	1.07	289	3.55	14	0.17	15	0.18
≥150	5,412	35332.68	311	8.80	62	1.75	232	6.57	6	0.17	11	0.31
HDL-C (mg/dl) **												
Abnormal	5,684	37372.54	268	7.17	50	1.34	204	5.46	5	0.13	9	0.24
Normal	11,781	78407.84	441	5.62	98	1.25	312	3.98	14	0.18	17	0.22
Blood pressure (mm/Hg)***												
Normal	10,869	71713.89	440	6.14	94	1.31	321	4.48	12	0.17	13	0.18
Elevated risk	2,858	19152.31	127	6.63	23	1.20	91	4.75	7	0.37	6	0.31
Hypertension	3,863	25865.86	149	5.76	32	1.24	109	4.21	1	0.04	7	0.27
Glucose (mg/dl)												
<100	11,974	78755.06	454	5.76	90	1.14	332	4.22	13	0.17	19	0.24
100-125	3,907	26462.49	165	6.24	37	1.40	120	4.53	5	0.19	3	0.11
>125	1,709	11514.51	97	8.42	22	1.91	69	5.99	2	0.17	4	0.35
Meat												
Seldom	4,820	31984.38	171	5.35	38	1.19	127	3.97	3	0.09	3	0.09
Infrequent	11,904	78845.33	488	6.19	94	1.19	360	4.57	13	0.16	21	0.27
Frequent	829	5625.25	56	9.96	17	3.02	33	5.87	4	0.71	2	0.36
Vegetable												
Seldom	3,679	24216.53	172	7.10	42	1.73	124	5.12	1	0.04	5	0.21
Infrequent	13,469	89529.87	527	5.89	105	1.17	384	4.29	19	0.21	19	0.21
Frequent	308	2045.50	6	2.93	0	0.00	6	2.93	0	0.00	0	0.00

Fruit												
Seldom	1,608	10685.41	102	9.55	20	1.87	75	7.02	2	0.19	5	0.47
Infrequent	7,190	47575.85	333	7.00	74	1.56	233	4.90	10	0.21	16	0.34
Frequent	8,773	58318.08	280	4.80	55	0.94	212	3.64	8	0.14	5	0.09

OSF: oral submucosa fibrosis; ***Quit**: Quit betel quid chewing, quit smoking or quit alcohol drinking defined as who had ever these oral habits; however no longer have these habit at the day of interview.

****HDL-C:** Abnormal defined as (Male with 0<HDL<40) or (Female with 0<HDL<50), Normal defined as (Male with 40<=HDL) or (Female with50<=HDL)

*****Hypertension**: Normal defined as systolic blood pressure (sbp)<130 or diastolic blood pressure (dbp)<85, Elevated risk defined as 130<=sbp<140 or 85<=dbp<90, Hypertension defined as sbp≥140 or dbp≥90

Table 2 The association between MetS, other factors and oral potentially malignant disorders (MetS → OPMD)

	RR	95% CI		aRR	95% CI	
Metabolic syndrome						
Yes vs No	1.42	1.22	1.66	1.33	1.14	1.55
Sex						
Male vs Female	7.14	3.94	12.94	3.49	1.89	6.44
Age groups (vs 70+)						
30-39	2.89	1.85	4.52	2.17	1.35	3.47
40-49	3.53	2.43	5.12	2.63	1.79	3.85
50-59	3.63	2.52	5.24	3.10	2.14	4.49
60-69	2.85	1.95	4.16	2.53	1.73	3.71
Betel nut chewing (vs Never)						
Quit*	3.03	2.54	3.63	2.00	1.62	2.47
Current	4.92	4.10	5.89	2.68	2.16	3.33
Cigarette smoking (vs Never)						
Quit*	2.32	1.78	3.03	1.31	0.96	1.78
Current	4.90	3.94	6.09	2.47	1.90	3.20
Alcohol drinking (vs Never)						
Quit*	2.18	1.62	2.92	1.23	0.90	1.68
Current	1.95	1.65	2.30	1.03	0.86	1.23
Meat (vs Seldom)						
Infrequent	1.13	0.95	1.35	0.95	0.79	1.13
Frequent	1.77	1.30	2.41	1.23	0.90	1.68
Vegetable (vs Seldom)						
Infrequent	0.83	0.70	0.99	0.92	0.77	1.10
Frequent	0.36	0.15	0.87	0.46	0.19	1.11
Fruit (vs Seldom)						
Infrequent	0.74	0.59	0.93	0.91	0.72	1.15
Frequent	0.51	0.40	0.64	0.79	0.62	1.00
Education level (vs Junior high school or lower)						
Senior high school	1.00	0.84	1.19	0.97	0.80	1.17
University	0.60	0.45	0.81	0.84	0.62	1.14

aRR: adjusted rate ratio; **CI**: confidence interval; ***Quit:** quit betel quid chewing, quit smoking or quit alcohol drinking defined as who had ever these oral habits; however no longer have these habits at the day of interview.

Table 3 The effect of metabolic syndrome components on oral potentially malignant disorders

	All OPMD			
	aRR*	**95% CI**		**p-value**
Component of metabolic syndrome				
Central obesity	1.22	1.04	1.44	0.0162
Hyper-triglyceride	1.26	1.07	1.49	0.0066
Low HDL-C	1.12	0.95	1.32	0.1851
Elevated blood pressure	0.93	0.79	1.09	0.3586
Hyperglycemia	1.20	1.02	1.41	0.0297
Metabolic syndrome score	1.14	1.08	1.20	<.0001

aRR: adjusted rate ratio; **CI**: confidence interval.

* adjusted rate ratio for components of metabolic syndrome and metabolic syndrome score were treated in different models with adjustment of age, sex, education level, betel nut chewing, cigarette smoking, alcohol drinking, meat, vegetable and fruit consumption.

Table 4 The association between metabolic syndrome and sub-types of oral potentially malignant disorders using multi-variable Poisson regression

	Leukoplakia			OSF			Verrucous hyperplasia			Erythroplakia + Erythroleukoplakia		
	aRR*	95% CI		aRR**	95% CI		aRR***	95% CI		aRR***	95% CI	
Metabolic syndrome												
Yes vs No	1.37	1.14	1.64	1.22	0.87	1.71	1.33	0.51	3.46	1.59	0.67	3.75
Component of metabolic syndrome												
Central obesity	1.30	1.07	1.57	1.06	0.74	1.52	1.17	0.47	2.89	0.94	0.37	2.36
Hyper-triglyceride	1.29	1.06	1.57	1.21	0.83	1.76	0.98	0.40	2.40	1.39	0.54	3.58
Low HDL-C	1.17	0.97	1.42	0.94	0.64	1.38	0.79	0.31	1.99	1.18	0.47	2.97
Elevated blood pressure	0.90	0.75	1.09	0.95	0.66	1.37	1.34	0.46	3.85	1.22	0.50	3.00
Hyperglycemia	1.16	0.96	1.41	1.43	0.99	2.05	1.28	0.52	3.19	0.99	0.37	2.64
Metabolic syndrome score	1.16	1.09	1.24	1.10	0.98	1.24	1.02	0.68	1.54	1.13	0.83	1.55

aRR: adjusted rate ratio; **CI**: confidence interval; **OSF**: oral submucous fibrosis

* adjusted rate ratio for metabolic syndrome, components of metabolic syndrome, and metabolic syndrome score were treated in different models with adjustment of age, sex, education level, betel nut chewing, cigarette smoking, alcohol drinking, meat, vegetable and fruit consumption.

** adjusted rate ratio for metabolic syndrome, components of metabolic syndrome, and metabolic syndrome score were treated in different models with adjustment of age, sex, education level, betel nut chewing, cigarette smoking, alcohol drinking, meat, and fruit consumption.

*** adjusted rate ratio for metabolic syndrome, components of metabolic syndrome, and metabolic syndrome score were treated in different models with adjustment of betel nut chewing and cigarette smoking.

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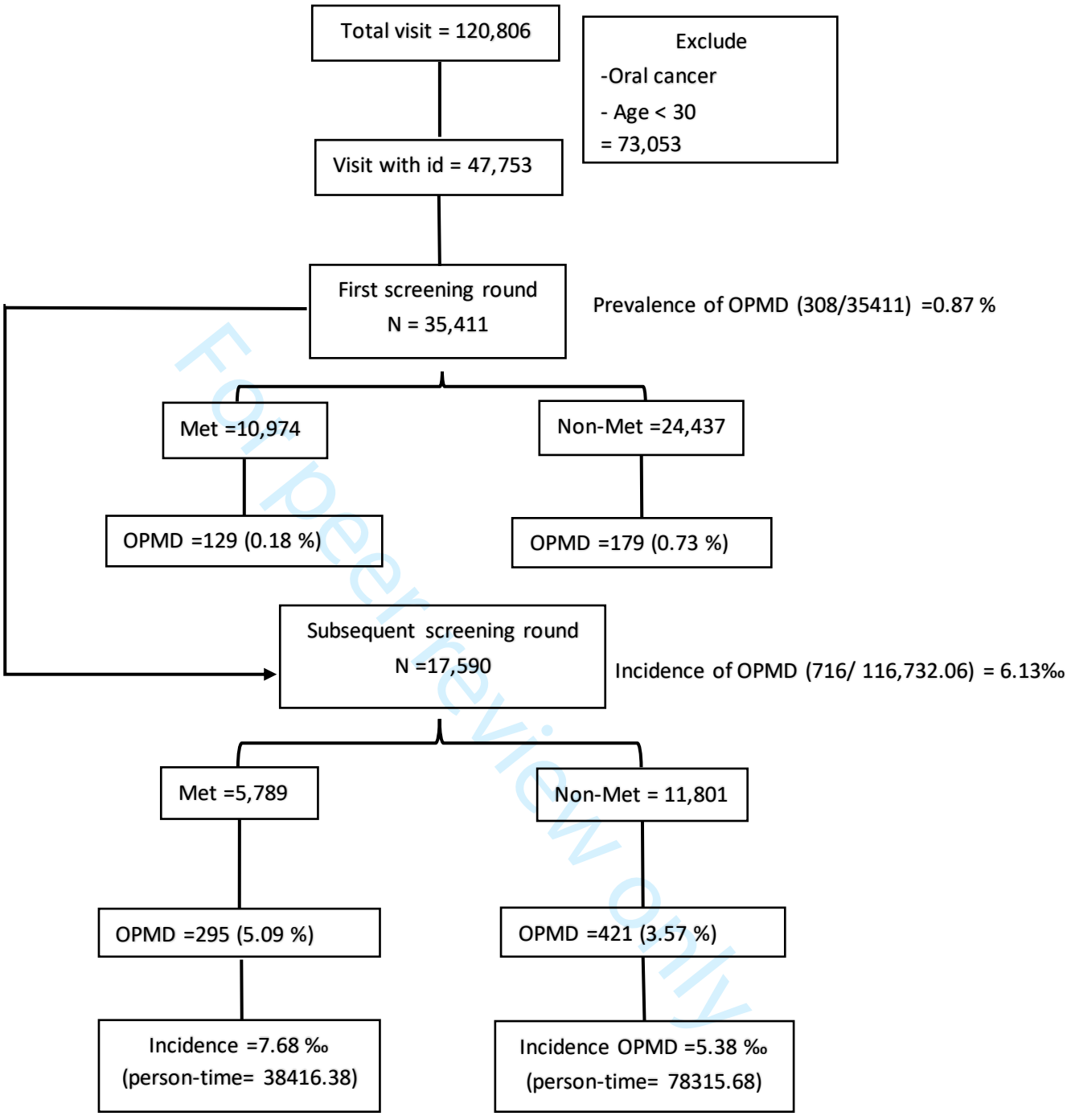

Figure 1 The flow chart for prospective normal cohort study design

Supplement Table 1 The association between MetS, other factors and prevalence of oral potentially malignant disorders

	OR	95%CI		aOR	95%CI	
Metabolic syndrome						
Yen vs No	1.61	1.28	2.02	1.44	1.14	1.82
Sex						
Male vs Female	7.32	4.65	11.53	2.50	1.50	4.16
Age groups (vs 70+)						
30-39	0.83	0.39	1.77	0.87	0.39	1.92
40-49	1.69	1.02	2.77	1.33	0.79	2.25
50-59	2.52	1.58	4.04	2.23	1.38	3.62
60-69	1.83	1.11	3.01	1.73	1.04	2.86
Betel nut chewing (vs Never)						
Quit*	3.33	2.53	4.37	1.40	1.04	1.90
Current	5.71	4.34	7.52	2.00	1.47	2.74
Cigarette smoking (vs Never)						
Quit*	4.72	3.23	6.91	2.66	1.72	4.12
Current	8.89	6.48	12.19	4.74	3.25	6.92
Alcohol drinking (vs Never)						
Quit*	2.49	1.95	3.16	0.98	0.59	1.63
Current	2.62	1.62	4.24	1.01	0.77	1.32
Meat (vs Seldom)						
Infrequent	1.28	0.98	1.67	1.00	0.76	1.32
Frequent	2.85	1.83	4.45	1.67	1.06	2.63
Vegetable (vs Seldom)						
Infrequent	0.82	0.63	1.07	0.88	0.68	1.16
Frequent	0.48	0.15	1.52	0.53	0.17	1.71
Fruit (vs Seldom)						
Infrequent	0.71	0.49	1.02	1.00	0.68	1.46
Frequent	0.54	0.38	0.78	1.02	0.69	1.50
Education level (vs Junior high school or lower)						
Senior high school	1.00	0.77	1.29	1.06	0.80	1.41
University	0.54	0.36	0.82	0.84	0.55	1.30

aOR: adjusted odds ratio; **CI**: confidence interval; ***Quit**: Quit betel quid chewing, quit smoking or quit alcohol drinking defined as who had ever have these oral habits; however no longer have these habits at the day of interview.

Supplement Table 2 The association between Component of MetS, other factors and oral potentially malignant disorders (MetS → OPMD)

	RR	95% CI		aRR	95% CI	
Component of metabolic syndrome						
Central obesity	1.36	1.17	1.58	1.22	1.04	1.44
Hyper-triglyceride	1.78	1.53	2.07	1.26	1.07	1.49
Low HDL-C	1.26	1.08	1.47	1.12	0.95	1.32
Elevated blood pressure	1.00	0.86	1.17	0.93	0.79	1.09
Hyperglycemia	1.21	1.04	1.42	1.20	1.02	1.41
Sex						
Male vs Female	7.14	3.94	12.94	3.57	1.94	6.59
Age groups (vs 70+)						
30-39	2.89	1.85	4.52	2.19	1.34	3.56
40-49	3.53	2.43	5.12	2.65	1.78	3.94
50-59	3.63	2.52	5.24	3.12	2.13	4.58
60-69	2.85	1.95	4.16	2.56	1.73	3.79
Betel nut chewing (vs Never)						
Quit*	3.03	2.54	3.63	1.94	1.57	2.40
Current	4.92	4.10	5.89	2.59	2.08	3.22
Cigarette smoking (vs Never)						
Quit*	2.32	1.78	3.03	1.32	0.96	1.79
Current	4.90	3.94	6.09	2.42	1.86	3.14
Alcohol drinking (vs Never)						
Quit*	2.18	1.62	2.92	1.24	0.90	1.70
Current	1.95	1.65	2.30	1.03	0.86	1.24
Meat (vs Seldom)						
Infrequent	1.13	0.95	1.35	0.94	0.79	1.13
Frequent	1.77	1.30	2.41	1.22	0.90	1.67
Vegetable (vs Seldom)						
Infrequent	0.83	0.70	0.99	0.93	0.78	1.12
Frequent	0.36	0.15	0.87	0.48	0.20	1.14
Fruit (vs Seldom)						
Infrequent	0.74	0.59	0.93	0.91	0.72	1.15
Frequent	0.51	0.40	0.64	0.77	0.60	0.98
Education level (vs Junior high school or lower)						
Senior high school	1.00	0.84	1.19	0.98	0.81	1.19
University	0.60	0.45	0.81	0.84	0.62	1.14

aRR: adjusted rate ratio; **CI**: confidence interval; ***Quit**: Quit betel quid chewing, quit smoking or quit alcohol drinking defined as who had ever have these oral habits; however no longer have these habits at the day of interview.

Supplement Table 3 The association between MetS score, other factors and oral potentially malignant disorders (MetS → OPMD)

	RR	95%CI		aRR	95%CI	
Metabolic syndrome						
Score	1.18	1.12	1.24	1.14	1.08	1.20
Sex						
Male vs Female	7.14	3.94	12.94	3.51	1.90	6.47
Age groups (vs 70+)						
30-39	2.89	1.85	4.52	2.18	1.36	3.50
40-49	3.53	2.43	5.12	2.64	1.80	3.87
50-59	3.63	2.52	5.24	3.09	2.13	4.48
60-69	2.85	1.95	4.16	2.53	1.73	3.70
Betel nut chewing (vs Never)						
Quit*	3.03	2.54	3.63	1.98	1.61	2.44
Current	4.92	4.10	5.89	2.63	2.12	3.27
Cigarette smoking (vs Never)						
Quit*	2.32	1.78	3.03	1.31	0.96	1.79
Current	4.90	3.94	6.09	2.48	1.91	3.22
Alcohol drinking (vs Never)						
Quit*	2.18	1.62	2.92	1.23	0.90	1.68
Current	1.95	1.65	2.30	1.03	0.86	1.23
Meat (vs Seldom)						
Infrequent	1.13	0.95	1.35	0.95	0.79	1.14
Frequent	1.77	1.30	2.41	1.23	0.90	1.68
Vegetable (vs Seldom)						
Infrequent	0.83	0.70	0.99	0.92	0.77	1.10
Frequent	0.36	0.15	0.87	0.46	0.19	1.11
Fruit (vs Seldom)						
Infrequent	0.74	0.59	0.93	0.92	0.73	1.15
Frequent	0.51	0.40	0.64	0.79	0.62	1.01
Education level (vs Junior high school or lower)						
Senior high school	1.00	0.84	1.19	0.97	0.81	1.17
University	0.60	0.45	0.81	0.84	0.62	1.14

aRR: adjusted rate ratio; **CI**: confidence interval; ***Quit**: Quit betel quid chewing, quit smoking or quit alcohol drinking defined as who had ever have these oral habits; however no longer have these habits at the day of interview.

Supplement Table 4 The association between MetS, other factors and oral submucous fibrosis (MetS → OSF)

	RR	95%CI		aRR	95%CI	
Metabolic syndrome						
Yen vs No	1.35	0.96	1.90	1.22	0.87	1.71
Sex						
Male vs Female	8.16	2.02	32.94	3.34	0.78	14.26
Age groups (vs 70+**)**						
30-39	2.88	1.23	6.73	2.61	1.04	6.54
40-49	2.60	1.26	5.34	2.08	0.97	4.47
50-59	2.22	1.08	4.56	1.99	0.96	4.13
60-69	2.25	1.08	4.69	2.07	0.99	4.33
Betel nut chewing (vs Never)						
Quit*	5.31	3.49	8.06	3.71	2.23	6.16
Current	7.82	5.07	12.05	4.77	2.87	7.92
Cigarette smoking (vs Never)						
Quit*	3.58	2.03	6.34	1.60	0.77	3.32
Current	5.10	3.07	8.47	1.96	1.04	3.66
Alcohol drinking (vs Never)						
Quit*	1.78	0.90	3.53	0.72	0.35	1.47
Current	1.80	1.25	2.59	0.83	0.56	1.23
Meat (vs Seldom)						
Infrequent	1.03	0.69	1.52	0.84	0.56	1.24
Frequent	2.65	1.47	4.77	1.71	0.94	3.11
Fruit (vs Seldom)						
Infrequent	0.92	0.54	1.56	1.11	0.65	1.91
Frequent	0.55	0.32	0.95	0.87	0.50	1.51
Education level (vs Junior high school or lower)						
Senior high school	1.11	0.76	1.61	1.07	0.70	1.62
University	0.23	0.08	0.62	0.33	0.12	0.94

aRR: adjusted rate ratio; **CI**: confidence interval ***Quit**: Quit betel quid chewing, quit smoking or quit alcohol drinking defined as who had ever have these oral habits; however no longer have these habits at the day of interview.

Supplement Table 5 The association between Component of MetS, other factors and oral submucous fibrosis (MetS → OSF)

	RR	95%CI		aRR	95%CI	
Component of metabolic syndrome						
Central obesity	1.21	0.87	1.70	1.06	0.74	1.52
Hyper-triglyceride	1.67	1.19	2.34	1.21	0.83	1.76
Low HDL-C	1.06	0.74	1.50	0.94	0.64	1.38
Elevated blood pressure	1.04	0.74	1.47	0.95	0.66	1.37
Hyperglycemia	1.37	0.97	1.92	1.43	0.99	2.05
Sex						
Male vs Female	8.16	2.02	32.94	3.27	0.77	13.93
Age groups (vs 70+**)**						
30-39	2.88	1.23	6.73	2.60	1.02	6.63
40-49	2.60	1.26	5.34	2.05	0.95	4.43
50-59	2.22	1.08	4.56	1.89	0.91	3.91
60-69	2.25	1.08	4.69	2.03	0.97	4.26
Betel nut chewing (vs Never)						
Quit*	5.31	3.49	8.06	3.77	2.26	6.31
Current	7.82	5.07	12.05	4.88	2.92	8.14
Cigarette smoking (vs Never)						
Quit*	3.58	2.03	6.34	1.59	0.77	3.29
Current	5.10	3.07	8.47	1.91	1.02	3.59
Alcohol drinking (vs Never)						
Quit*	1.78	0.90	3.53	0.73	0.36	1.50
Current	1.80	1.25	2.59	0.84	0.56	1.25
Meat (vs Seldom)						
Infrequent	1.03	0.69	1.52	0.82	0.55	1.21
Frequent	2.65	1.47	4.77	1.67	0.91	3.09
Fruit (vs Seldom)						
Infrequent	0.92	0.54	1.56	1.12	0.65	1.92
Frequent	0.55	0.32	0.95	0.85	0.49	1.48
Education level (vs Junior high school or lower)						
Senior high school	1.11	0.76	1.61	1.09	0.71	1.66
University	0.23	0.08	0.62	0.34	0.12	0.95

aRR: adjusted rate ratio; **CI**: confidence interval; ***Quit**: Quit betel quid chewing, quit smoking or quit alcohol drinking defined as who had ever have these oral habits; however no longer have these habits at the day of interview.

Supplement Table 6 The association between MetS score, other factors and oral submucous fibrosis (MetS → OSF)

	RR	95%CI		aRR	95%CI	
Metabolic syndrome						
Score	1.15	1.03	1.30	1.10	0.98	1.24
Sex						
Male vs Female	8.16	2.02	32.94	3.37	0.79	14.38
Age groups (vs 70+)						
30-39	2.88	1.23	6.73	2.63	1.05	6.62
40-49	2.60	1.26	5.34	2.10	0.98	4.50
50-59	2.22	1.08	4.56	1.99	0.96	4.12
60-69	2.25	1.08	4.69	2.07	0.99	4.33
Betel nut chewing (vs Never)						
Quit*	5.31	3.49	8.06	3.68	2.21	6.11
Current	7.82	5.07	12.05	4.70	2.83	7.80
Cigarette smoking (vs Never)						
Quit*	3.58	2.03	6.34	1.60	0.77	3.33
Current	5.10	3.07	8.47	1.96	1.05	3.67
Alcohol drinking (vs Never)						
Quit*	1.78	0.90	3.53	0.72	0.35	1.47
Current	1.80	1.25	2.59	0.83	0.56	1.23
Meat (vs Seldom)						
Infrequent	1.03	0.69	1.52	0.84	0.57	1.24
Frequent	2.65	1.47	4.77	1.71	0.94	3.11
Fruit (vs Seldom)						
Infrequent	0.92	0.54	1.56	1.12	0.65	1.92
Frequent	0.55	0.32	0.95	0.87	0.50	1.51
Education level (vs Junior high school or lower)						
Senior high school	1.11	0.76	1.61	1.07	0.70	1.63
University	0.23	0.08	0.62	0.33	0.12	0.94

aRR: adjusted rate ratio; **CI**: confidence interval; ***Quit**: Quit betel quid chewing, quit smoking or quit alcohol drinking defined as who had ever have these oral habits; however no longer have these habits at the day of interview.

Supplement Table 7 The association between MetS, other factors and Leukoplakia (MetS → Leukoplakia)

	RR	95%CI		aRR	95%CI	
Metabolic syndrome						
Yen vs No	1.45	1.22	1.73	1.37	1.14	1.64
Sex						
Male vs Female	6.48	3.36	12.52	3.29	1.67	6.48
Age groups (vs 70+)						
30-39	2.92	1.63	5.22	2.08	1.13	3.81
40-49	4.38	2.72	7.05	3.20	1.97	5.18
50-59	4.86	3.04	7.78	4.09	2.55	6.57
60-69	3.51	2.16	5.71	3.13	1.92	5.09
Betel nut chewing (vs Never)						
Quit*	2.70	2.20	3.33	1.81	1.42	2.30
Current	4.45	3.61	5.49	2.42	1.88	3.12
Cigarette smoking (vs Never)						
Quit*	2.04	1.49	2.80	1.22	0.86	1.74
Current	4.88	3.80	6.27	2.66	1.98	3.58
Alcohol drinking (vs Never)						
Quit*	2.29	1.63	3.20	1.36	0.95	1.96
Current	1.95	1.61	2.36	1.06	0.86	1.31
Meat (vs Seldom)						
Infrequent	1.12	0.91	1.37	0.93	0.76	1.15
Frequent	1.47	1.00	2.16	1.01	0.68	1.51
Vegetable (vs Seldom)						
Infrequent	0.84	0.69	1.03	0.93	0.75	1.14
Frequent	0.49	0.20	1.19	0.60	0.25	1.45
Fruit (vs Seldom)						
Infrequent	0.68	0.53	0.89	0.85	0.65	1.11
Frequent	0.51	0.39	0.66	0.78	0.59	1.03
Education level (vs Junior high school or lower)						
Senior high school	0.99	0.80	1.22	0.98	0.78	1.22
University	0.74	0.55	1.01	1.03	0.74	1.43

aRR: adjusted rate ratio; **CI**: confidence interval; ***Quit**: Quit betel quid chewing, quit smoking or quit alcohol drinking defined as who had ever have these oral habits; however no longer have these habits at the day of interview.

Supplement Table 8 The association between Component of MetS, other factors and Leukoplakia (MetS → Leukoplakia)

	RR	95%CI		aRR	95%CI	
Component of metabolic syndrome						
Central obesity	1.43	1.20	1.70	1.30	1.07	1.57
Hyper-triglyceride	1.85	1.56	2.21	1.29	1.06	1.57
Low HDL-C	1.34	1.12	1.60	1.17	0.97	1.42
Elevated blood pressure	0.99	0.83	1.18	0.90	0.75	1.09
Hyperglycemia	1.20	1.00	1.44	1.16	0.96	1.41
Sex						
Male vs Female	6.48	3.36	12.52	3.43	1.74	6.75
Age groups (vs 70+)						
30-39	2.92	1.63	5.22	2.15	1.14	4.06
40-49	4.38	2.72	7.05	3.34	2.00	5.57
50-59	4.86	3.04	7.78	4.30	2.61	7.08
60-69	3.51	2.16	5.71	3.29	1.97	5.49
Betel nut chewing (vs Never)						
Quit*	2.70	2.20	3.33	1.73	1.36	2.20
Current	4.45	3.61	5.49	2.31	1.79	2.98
Cigarette smoking (vs Never)						
Quit*	2.04	1.49	2.80	1.23	0.86	1.75
Current	4.88	3.80	6.27	2.60	1.93	3.50
Alcohol drinking (vs Never)						
Quit*	2.29	1.63	3.20	1.37	0.95	1.98
Current	1.95	1.61	2.36	1.06	0.86	1.32
Meat (vs Seldom)						
Infrequent	1.12	0.91	1.37	0.94	0.76	1.16
Frequent	1.47	1.00	2.16	1.02	0.68	1.51
Vegetable (vs Seldom)						
Infrequent	0.84	0.69	1.03	0.92	0.75	1.14
Frequent	0.49	0.20	1.19	0.60	0.25	1.45
Fruit (vs Seldom)						
Infrequent	0.68	0.53	0.89	0.85	0.65	1.11
Frequent	0.51	0.39	0.66	0.78	0.59	1.03
Education level (vs Junior high school or lower)						
Senior high school	0.99	0.80	1.22	0.98	0.78	1.22
University	0.74	0.55	1.01	1.04	0.75	1.44

aRR: adjusted rate ratio; **CI**: confidence interval; ***Quit**: Quit betel quid chewing, quit smoking or quit alcohol drinking defined as who had ever have these oral habits; however no longer have these habits at the day of interview.

Supplement Table 9 The association between MetS score, other factors and Leukoplakia (MetS → Leukoplakia)

	RR	95%CI		aRR	95%CI	
Metabolic syndrome						
Score	1.20	1.13	1.27	1.16	1.09	1.24
Sex						
Male vs Female	6.48	3.36	12.52	3.31	1.68	6.51
Age groups (vs 70+)						
30-39	2.92	1.63	5.22	2.09	1.14	3.84
40-49	4.38	2.72	7.05	3.22	1.99	5.22
50-59	4.86	3.04	7.78	4.08	2.54	6.54
60-69	3.51	2.16	5.71	3.12	1.92	5.08
Betel nut chewing (vs Never)						
Quit*	2.70	2.20	3.33	1.79	1.40	2.27
Current	4.45	3.61	5.49	2.37	1.84	3.05
Cigarette smoking (vs Never)						
Quit*	2.04	1.49	2.80	1.22	0.86	1.74
Current	4.88	3.80	6.27	2.68	1.99	3.60
Alcohol drinking (vs Never)						
Quit*	2.29	1.63	3.20	1.37	0.95	1.97
Current	1.95	1.61	2.36	1.05	0.85	1.30
Meat (vs Seldom)						
Infrequent	1.12	0.91	1.37	0.94	0.76	1.16
Frequent	1.47	1.00	2.16	1.02	0.68	1.51
Vegetable (vs Seldom)						
Infrequent	0.84	0.69	1.03	0.92	0.75	1.14
Frequent	0.49	0.20	1.19	0.60	0.25	1.45
Fruit (vs Seldom)						
Infrequent	0.68	0.53	0.89	0.85	0.65	1.11
Frequent	0.51	0.39	0.66	0.78	0.59	1.03
Education level (vs Junior high school or lower)						
Senior high school	0.99	0.80	1.22	0.98	0.78	1.22
University	0.74	0.55	1.01	1.04	0.75	1.44

aRR: adjusted rate ratio; **CI**: confidence interval; ***Quit**: Quit betel quid chewing, quit smoking or quit alcohol drinking defined as who had ever have these oral habits; however no longer have these habits at the day of interview.

Supplement Table 10 The association between MetS, other factors and Verrucous hyperplasia (MetS → Verrucous hyperplasia)

	RR	95%CI		aRR	95%CI	
Metabolic syndrome						
Yen vs No	1.32	0.51	3.40	1.33	0.51	3.46
Betel nut chewing (vs Never)						
Quit*	1.92	0.64	5.71	1.24	0.40	3.82
Current	2.71	0.84	8.81	1.13	0.34	3.74
Cigarette smoking (vs Never)						
Quit*	1.91	0.12	30.49	1.72	0.09	31.37
Current	17.03	2.26	128.38	15.80	2.04	122.28

aRR: adjusted rate ratio; **CI**: confidence interval; ***Quit**: Quit betel quid chewing or quit smoking drinking defined as who had ever have these oral habits; however no longer have these habits at the day of interview.

Supplement Table 11 The association between Component of MetS, other factors and Verrucous hyperplasia (MetS → Verrucous hyperplasia)

	RR	95%CI		aRR	95%CI	
Component of metabolic syndrome						
Central obesity	1.05	0.41	2.71	1.17	0.47	2.89
Hyper-triglyceride	1.26	0.47	3.42	0.98	0.40	2.40
Low HDL-C	0.88	0.31	2.50	0.79	0.31	1.99
Elevated blood pressure	1.04	0.40	2.69	1.34	0.46	3.85
Hyperglycemia	1.13	0.42	3.05	1.28	0.52	3.19
Betel nut chewing (vs Never)						
Quit*	1.92	0.64	5.71	1.22	0.39	3.80
Current	2.71	0.84	8.81	0.84	0.23	3.13
Cigarette smoking (vs Never)						
Quit*	1.91	0.12	30.49	1.72	0.09	31.29
Current	17.03	2.26	128.38	16.34	2.00	133.78

aRR: adjusted rate ratio; **CI**: confidence interval; ***Quit**: Quit betel quid chewing or quit smoking defined as who had ever have these oral habits; however no longer have these habits at the day of interview.

Supplement Table 12 The association between MetS score, other factors and Verrucous hyperplasia (MetS → Verrucous hyperplasia)

	RR	95%CI		aRR	95%CI	
Metabolic syndrome						
Score	1.01	0.67	1.54	1.02	0.68	1.54
Betel nut chewing (vs Never)						
Quit*	1.92	0.64	5.71	1.24	0.40	3.85
Current	2.71	0.84	8.81	1.15	0.34	3.91
Cigarette smoking (vs Never)						
Quit*	1.91	0.12	30.49	1.73	0.09	31.58
Current	17.03	2.26	128.38	15.73	2.01	122.98

aRR: adjusted rate ratio; **CI**: confidence interval; ***Quit**: Quit betel quid chewing or quit smoking defined as who had ever have these oral habits; however no longer have these habits at the day of interview.

Supplement Table 13 The association between MetS, other factors and Erythroplaklia + Erythroleukoplakia (MetS → Erythroplakia + Erythroleukoplakia)

	RR	95%CI		aRR	95%CI	
Metabolic syndrome						
Yen vs No	1.88	0.80	4.43	1.59	0.67	3.75
Betel nut chewing (vs Never)						
Quit*	4.31	1.16	16.03	4.47	0.93	21.46
Current	18.24	5.88	56.54	17.81	4.95	64.12
Cigarette smoking (vs Never)						
Quit*	1.91	0.48	7.62	0.84	0.15	4.60
Current	3.46	1.13	10.61	0.96	0.26	3.49

aRR: adjusted rate ratio; **CI**: confidence interval; ***Quit**: Quit betel quid chewing or quit smoking defined as who had ever have these oral habits; however no longer have these habits at the day of interview.

Supplement Table 14 The association between Component of MetS, other factors and Erythroplaklia + Erythroleukoplakia (MetS → Erythroplakia + Erythroleukoplakia)

	RR	95%CI		aRR	95%CI	
Component of metabolic syndrome						
Central obesity	1.24	0.52	2.94	0.94	0.37	2.36
Hyper-triglyceride	2.10	0.89	4.95	1.39	0.54	3.58
Low HDL-C	1.30	0.54	3.13	1.18	0.47	2.97
Elevated blood pressure	1.33	0.54	3.29	1.22	0.50	3.00
Hyperglycemia	1.03	0.42	2.56	0.99	0.37	2.64
Betel nut chewing (vs Never)						
Quit*	4.31	1.16	16.03	4.49	0.94	21.55
Current	18.24	5.88	56.54	17.86	5.10	62.54
Cigarette smoking (vs Never)						
Quit*	1.91	0.48	7.62	0.85	0.15	4.65
Current	3.46	1.13	10.61	0.91	0.24	3.50

aRR: adjusted rate ratio; **CI**: confidence interval; ***Quit**: Quit betel quid chewing or quit smoking defined as who had ever have these oral habits; however no longer have these habits at the day of interview.

Supplement Table 15 The association between MetS score, other factors and Erythroplaklia + Erythroleukoplakia (MetS → Erythroplakia + Erythroleukoplakia)

	RR	95%CI		aRR	95%CI	
Metabolic syndrome						
Score	1.22	0.89	1.68	1.13	0.83	1.55
Betel nut chewing (vs Never)						
Quit*	4.31	1.16	16.03	4.49	0.94	21.54
Current	18.24	5.88	56.54	17.92	4.96	64.68
Cigarette smoking (vs Never)						
Quit*	1.91	0.48	7.62	0.84	0.15	4.60
Current	3.46	1.13	10.61	0.95	0.26	3.49

aRR: adjusted rate ratio; **CI**: confidence interval; ***Quit**: Quit betel quid chewing or quit smoking defined as who had ever have these oral habits; however no longer have these habits at the day of interview.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Pages
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5,6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7,8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7,8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7,8
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8,10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	11 (Figure)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted	11,12

		estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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The Effect of Metabolic Syndrome on Incidence of Oral Potentially Malignant Disorder: A Prospective Cohort Study in Taiwan

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The Effect of Metabolic Syndrome on Incidence of Oral Potentially Malignant Disorder: A Prospective Cohort Study in Taiwan

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Abstract

Objectives We aimed to assess the effect of metabolic syndrome (MetS) on incident oral potentially malignant disorder (OPMD).

Design We conducted a prospective cohort study of the Changhua community-based integrated screening (CHCIS) programme and nationwide oral cancer screening programme during the period between 2005 and 2014.

Setting Changhua community-based integrated screening CHCIS, Taiwan.

Participants We enrolled 17,590 participants aged 30 years and older.

Main outcomes and measures We assessed the impact of MetS on the outcome measured by incident OPMD.

Results: The incidences of OPMD among subjects with and without MetS were 7.68 ‰ and 5.38 ‰, respectively. After adjusting for confounders, subjects with MetS exhibited a statistically greater risk of developing OPMD compared with those who were free of MetS by 33% (aRR=1.33, 95% CI: 1.14-1.55). Individual components of MetS still remained significant, including central obesity (aRR=1.22, 95% CI: 1.04-1.44), hypertriglyceridaemia (aRR=1.26, 95% CI: 1.07-1.49), and hyperglycaemia (aRR=1.20, 95% CI: 1.02-1.41). Central obesity and hypertriglyceridaemia were also statistically associated with a sub-type of OPMD, namely, leukoplakia.

Conclusion: The temporal influence of MetS on the risk of incident OPMD was noted in our prospective cohort study. Therefore, promoting a MetS prevention and control programme might reduce the occurrence of OPMD and oral cancer.

Strengths and limitations of this study

- A large population-based prospective cohort study was conducted to examine the impact of metabolic syndrome (MetS) on incident oral potentially malignant disorder (OPMD).
- This is the first study to investigate the effect of metabolic syndrome on incidence of OPMD as well as sub-types of OPMD, especially leukoplakia and oral submucous fibrosis.
- Investigations into other subtypes of OPMD are limited due to the rarity of other OPMD cases in our population.
- The results of our study are based on a Taiwanese population 30 years and older, so the generalization of our results to other regions would be limited especially given ethnic, genetic and dietary features.

Introduction

Oral potentially malignant disorder (OPMD) is an disorder that has potential for subsequent progression to oral cancer [1]. Thus, a better understanding of the risk factors for the occurrence of OPMD is important for the primary prevention of oral cancer [2]. Evidence on tobacco use, betel quid chewing, and alcohol drinking has well documented these major risk factors for OPMD [3-4]. Metabolic syndrome (MetS) is associated with the increased risk of several cancers, including oral cancer [5,6]. MetS is also associated with OPMD [7,8]. Such an association due to common shared underlying pathways (such as chronic inflammation) could be attributed to OPMD. Several studies have proposed the possible biological linkage between OPMD and MetS, which may have pro-inflammatory markers and insulin resistance in common [9-10]. However, the true biological causes accounting for such an association between MetS and OPMD remain elusive. In spite of this, it is still very worthwhile to study how MetS is associated with OPMD by clarifying the temporal relationship between MetS and OPMD. A prospective cohort study is therefore required.

In the Changhua community-based integrated screening (CHCIS) programme, a routine health check-up that embraces biomarker tests for MetS has been conducted annually since 2005 [11]. The early detection of OPMD and oral cancer has been provided under the instruction of nationwide oral cancer screening programme [12]. This screened cohort provides an opportunity to elucidate the effect of MetS on the incidence of OPMD with a normal cohort at baseline and followed over time until 2014.

Using empirical data from a large population-based integrated screening programme in combination with a nationwide oral cancer screening programme with oral visual inspection, the major aim of this study was to assess the temporal influence of MetS on OPMD.

Materials and methods

Study design

Our study design consists of two main steps. The first step is tailored for prevalence (cross-sectional design), and the second step is a longitudinal follow-up for incident cases of OPMD (Figure 1). We conducted cross-sectional analysis to determine the prevalence of OPMD among the MetS and MetS-free groups at baseline (identified at the first screening round) to create a normal cohort by excluding those who were diagnosed with OPMD or oral cancer before or at the first screening. Subjects in the normal cohort have undergone repeated screening continuously.

To address our initial hypothesis that MetS plays a role in the aetiology of OPMD, a prospective follow-up study was adopted. We followed the OPMD-free cohort who attended subsequent screenings in the nationwide oral cancer screening programme to identify those with an OPMD diagnosis in subsequent screening rounds. It should be noted that subjects may attend the CHCIS and nationwide oral cancer screening programme at different times. We defined the status of MetS of participants using the first screen in CHCIS and the first diagnosis of OPMD in the nationwide oral cancer screening programme.

Study population and data collection

The CHCIS programme is a population-based screening programme that followed the service model of the Keelung community-based integrated screening (KCIS) programme [13]. These programmes provided screening services of multiple cancers (liver cancer, breast cancer, colorectal cancer, oral cancer, and cervical cancer), chronic diseases (hyperlipidaemia, hypertension, and hyperglycaemia, and MetS), and anthropometric measurements [11]. The population in this study consists of dwellers aged 30 years or older that have been participated in

both CHCIS and the nationwide oral cancer screening programme between 2005 and 2014. Subjects who had a diagnosis of oral cancer before the first attendance to the CHCIS programme were excluded.

All participants were instructed to follow an 8-hour fasting before blood draw. Biochemical examination of fasting glucose and lipid profiles was performed. The anthropometric measures for body height, body weight, and circumferences of waist and hip were measured by either public health nurses or well-trained volunteer social workers in the community settings. All participants in the CHCIS programme were interviewed to obtain information on education level, oral habits (including betel nut chewing, cigarette smoking, and alcohol drinking), dietary habits, personal disease history, and family disease history. For oral habits, we classified the habit as never, quit, or current user. Quitting in our study refers to participants who reported habitual use of chewing betel quid, smoking cigarettes, or drinking alcohol; however, at the time of interview, they reported no regular consumption of betel quid, cigarettes, or alcohol. Dietary factors, including meat, vegetable and fruit consumption, were classified as seldom (including never), infrequent, and frequent. Infrequent meat consumption was defined as having 1-2 units per day, and frequent meat consumption was defined as 3-4 units per day. Infrequent vegetable consumption was defined as having a half or 1 bowl per day, and frequent vegetable consumption was defined as 3-4 bowls per day. Infrequent fruit consumption was defined as 1-4 times per week, and frequent fruit consumption was defined as more than 5 times per week.

Instruction on informed consent was first given and approved by those who expressed the willingness of participating in the study. This study was approved by the Institutional Review Board of Taipei Medical University (TMU-JIRB: N201611014)

OPMD detection

Since 2005, the oral visual inspection for all eligible participants was performed in Changhua County. In each on-site screening centre, trained dentists or physicians examined all participants. For those who were clinically diagnosed with oral leukoplakia, erythroleukoplakia, erythroplakia, oral submucous fibrosis (OSF), and verrucous hyperplasia were recorded as positive for OPMD.

Metabolic syndrome

Metabolic syndrome (MetS) was defined according to the Epidemiology Task Force Consensus Group criteria (2005) [14] in which participants presented at least three or more of the five components including: (1) central obesity (waist circumference $\geq$ 80 cm for females and $\geq$ 90 cm for males), (2) hypertriglyceridaemia ($\geq$ 150 mg/dl), (3) low level of high-density lipoprotein cholesterol (HDL-C) (<50 mg/dl for females and <40 mg/dl for males), (4) elevated blood pressure (systolic blood pressure $\geq$ 130 mm Hg or diastolic blood pressure $\geq$ 85 mm Hg), and (5) hyperglycaemia (fasting glucose $\geq$ 100 mg/dl).

Patient and Public Involvement

Participants in our study were recruited through the CHCIS programme. Participants were not involved in the design and conduct of the study. Staff in the Changhua County Public Health Bureau and local health centres were responsible for preparation and implementation of the screening service in the community.

The results of our study will be disseminated to the public through the Changhua County Public Health Bureau.

Statistical analysis

Prevalence of OPMD was presented as cases per 100 persons. The OPMD incidence rate was presented as cases per 1,000 person-years. The univariate Poisson regression model was first used to estimate the rate ratio (RR) for MetS and factors in association with the risk for developing OPMD. The adjusted rate ratio (aRR) was further estimated using the multi-variable Poisson regression model when significant confounding factors from the univariate analyses and other factors reported of having significant association with OPMD in previous studies were retained in the model. In addition to the dichotomous variable of MetS or not, we also examined the effect of each individual component of MetS and also the MetS score in separate models with both univariate and multivariate analyses. The magnitude of the effect between MetS and sub-types of OPMD was estimated in separate multi-variable Poisson regression models. Statistical significance was defined as $p<0.05$. All analyses were conducted with SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

A total of 35,411 subjects aged 30 years or older were included in this study from 2005 to 2014 in Changhua. The prevalence of OPMD was 0.87% (=306/35,411). The prevalence of MetS was 31% (=10,974/35,411) (Figure 1). Subjects with MetS had a statistically significantly 1.44-fold (95% CI: 1.14-1.82) increased risk to develop the risk for OPMD compared with those without MetS (see Supplementary Table 1).

The incidence of OPMD varies based on demographic and lifestyle factors (Table 1). The incidence of OPMD in subjects with MetS (7.68 per 1000 person-years) was increased compared with those who were free of MetS (5.38 per 1000 person-years). Male subjects aged between 40-59 years and those with increased body mass index (BMI), increased blood pressure, and elevated lipid profiles tended to exhibit an increased risk of OPMD compared with their complementary groups. A previous habit of betel quid chewing, smoking, and alcohol drinking were associated with an increased incidence of OPMD. High consumption of meat and lower consumption of vegetables and fruit were also related to higher risk of OPMD.

Table 2 shows the effect of MetS on the risk of OPMD. In univariate analysis, participants with MetS had a 42% increased risk of developing OPMD compared with those who were MetS free (RR=1.42, 95% CI: 1.22-1.66). Other factors were also associated with increased risks of developing OPMD, including male, age less than 70, betel nut chewing, cigarette smoking, alcohol drinking, meat consumption, and lower education level. In multivariable analysis, after adjusting for potential confounding factors, including age, sex, education level, betel nut chewing, cigarette smoking, meat consumption, vegetable consumption, the intake of fruit, and alcohol drinking, the association of MetS with an elevated risk of OPMD remained significant (aRR=1.33, 95% CI: 1.14-1.55).

In addition to exclusively focusing on MetS outcome, we also investigated the effects of individual components of MetS (Table 3). The results show that central obesity (aRR=1.22, 95% CI: 1.04-1.44), hypertriglyceridaemia (aRR=1.26, 95% CI: 1.07-1.49) and hyperglycaemia (aRR=1.20, 95% CI: 1.02-1.41) led to a statistically significant increased risk of OPMD. However, the effects of MetS components were different with respect to OPMD subtypes (Table 4). For leukoplakia, only central obesity (aRR=1.30, 95% CI: 1.07-1.57) and hypertriglyceridaemia (aRR=1.29, 95% CI: 1.06-1.57) remained significant. Only hyperglycaemia (aRR=1.43, 95% CI: 0.99-2.05) exhibited a borderline association with an increased risk for OSF. MetS led to a 33% elevated risk of verrucous hyperplasia, but it was not statistically significant due to the small number (aRR=1.33, 95% CI: 0.51-3.46). Same phenomenon was noted for erythroplakia and erythroleukoplakia (aRR=1.59, 95% CI: 0.67-3.75). We also provide detailed results on the effects of dichotomous MetS, individual components of MetS and MetS score for all OPMD cases (Supplementary Tables 2-3), leukoplakia (Supplementary Tables 4-6), OSF (Supplementary Tables 7-9), verrucous hyperplasia (Supplementary Tables 10-12), and erythroplakia and erythroleukoplakia (Supplementary Tables 13-15).

Discussion

In contrast to previous studies that place emphasis on the association between MetS and OPMD, the main objective of the present study, in addition to corroborating the association studies, was to investigate a temporal sequence pertaining to the effect of MetS on incident OPMD based on a longitudinal cohort study. A statistically significant impact of MetS on incident OPMD was observed. We used a longitudinal follow-up study design to address the limitation of the cross-sectional study design given that it cannot elucidate the temporal relationship between MetS and OPMD.

The association between MetS and OPMD has been elucidated in several previous cross-sectional studies conducted in Keelung community-based integrated screening programme (KCIS) and in Yunlin county, and MetS increased the risk of OPMD by 68% and 39%, respectively [7,8], which has been also confirmed in our current study. We also found that MetS led to a 44% increased risk associated with MetS for the presence of OPMD.

Furthermore, given its prospective cohort study design, our study further demonstrated the temporal effect of MetS and individual components on incident OPMD. Such a causal relationship between MetS and the risk for OPMD is independent of two well-established risk factors for oral pre-malignant lesions, namely smoking and betel quid chewing [3], [15], [16]. Applying such information to oral cancer screening would provide additional value for identifying a high-risk category of OPMD.

Regarding an independent contributory cause of MetS accounting for OPMD, the association between MetS and tumour progression in OPMD and oral cancer might be attributable to the common underlying mechanism, an inflammatory process or immune response for both outcomes. To our knowledge, the exact pathway linking MetS and OPMD remains

unclear. However, cytokines are often secreted by immune cells in response to inflammation. This process would lead an increased amount of C-reactive protein (CRP) [17]. CRP is known as a biomarker for cardiovascular disease. Recently, CRP was found to increase oxygen radicals [18]. These inflammatory factors can activate oncogenes and inactivate tumour suppressor genes and can potentially induce cell proliferation and prolong cell survival, which may result in genetic instability with an increased risk of cancer [19]. Previous studies proposed common shared mechanisms between MetS and OPMD, including pro-inflammatory markers (TNF-alpha, CRP, IL-6) and insulin resistance [9,10,20]. Therefore, MetS may affect cancer tumour cells through increased proliferation, angiogenesis and damage to the DNA molecule under chronic hyperglycaemia, insulin resistance and hyperinsulinemia [21-22]. In addition, MetS particularly with insulin resistance can overstimulate insulin growth factor-1 (IGF-1) and insulin receptor. An increasing and changing of IGF-1 signalling pathway and insulin receptor expression might also lead to an increased risk of cancer [17]. In the present study, we found that central obesity, hyperglycaemia, and hypertriglyceridemia were significant individual components of MetS responsible for the development of OPMD. Previous studies revealed that central obesity can stimulate insulin resistance, dyslipidaemia and systematic inflammation. The individual components were considered to play a vital role in the pathogenesis of certain type of cancers [23,24]. Moreover, insulin resistance was also associated with an increase in glucose and triglyceride production. Both were highly associated with the risk of developing OPMD in our analysis.

Betel quid's substances (nitrosated and arecal alkaloid derivatives) increase the risk of oral cancer and OPMD. This effect was not restricted to their direct contact tissue. Lee et al, found that betel quid chewing and components of MetS exhibit a positive correlation explained

by oxidative stress and inflammation [25]. An increase in the risk of oral cancer or OPMD by consuming betel quid and also cigarette smoking or alcohol drinking were noted in our study, even in patients who had quit these habits because they were exposed to these carcinogenesis components for a sufficient period. Our results were consistent with previous studies, which demonstrated that former or ex- consuming of these oral habits still had higher risk of oral cancer, leukoplakia and OSF compared with non-users[26, 27].

In addition to betel quid, foods were also of concern. Numerous studies unveiled that potential foods, such as red meat, were associated with increased IL-6 [28], and vegetable and fruit could lowered CRP [29]. In our study, we found that only high consumption of fruit was a protective factor of OPMD. Our findings were consistent with Fann et al, and Maserejian et al., who found that fruit decreased the risk of periodontal disease and OPMD, respectively [30,31]. Interestingly, fruit also reduced the risk of MetS [32]. Therefore, these findings support our hypothesis that inflammation is one of the potential mechanisms underlying the relationship between MetS and OPMD.

We examined the effect of MetS on OPMD subtypes and found that MetS was associated with an increased risk of leukoplakia but not other sub-types, including OSF, verrucous hyperplasia, and erythleukoplakia, due to the limited number of cases. Regarding leukoplakia, among the components of MetS, only central obesity and hypertriglyceridaemia significantly elevated the risk of leukoplakia. These results were inconsistent with the previous study that found that only hypertriglyceridaemia and hyperglycaemia significantly increased the risk of leukoplakia [8]. Regarding hypertriglyceridaemia in leukoplakia, a previous study reported significantly higher triglyceride levels in individuals with leukoplakia compared with healthy people [33]. Increasing triglyceride levels were possibly due to the excessive release of free fatty

acids, which resulted from insulin resistance. Moreover, insulin resistance can be stimulated by central obesity. In addition, Meisel et al, reported that visceral obesity was more likely to be found in people with leukoplakia compared with those without [34]. The aforementioned studies support our findings that two MetS components, including central obesity and hypertriglyceridaemia, are associated with leukoplakia. However, the mechanism remains unclear.

Although our study demonstrated that hyperglycaemia did not significantly increase the risk of OSF, the aRR exhibited the largest increased risk magnitude in OSF. Regarding OSF, it has been recognized that the development of fibrosis is pathologically responsible for tissue injury caused by chronic hyperglycaemia. The development of fibrosis was driven by the accumulation of extracellular matrix (ECM) [35].

One of the unique characteristics of OSF is the symptom of mouth opening restriction [36], [37,38]. A possible causation for restricted mouth opening might involve the dynamics of ECM deposited around muscle fibres in different stages of OSF, and these dynamics lead to the consequence of the loss of variety of ECM molecules, including elastin, and replacement with collagen type I muscle fibres [39]. Notably, it has been shown that hyperglycaemia can alter the collagenolysis [40] and also ECM's components interaction through advanced glycation end products (AGEs) modification [41-42]. These reasons mentioned above may support the borderline impact of hyperglycaemia on OSF and its symptom.

Another possibility of the discordance between these findings might be due to the differences in study approaches and communities with different dietary habits. However, both studies noted that hypertriglyceridaemia and hyperglycaemia were related to OPMD. In addition

to these biological aspects, these results are supported by the strong epidemiological study design in which we followed up the OPMD-free study population until the occurrence of OPMD.

In the view of oral cancer control, primary prevention aims to reduce the exposure to risk factors. In Taiwan, several cessation campaigns have been launched, but most of these efforts only considered conventional risk factors, including cigarette smoking and betel nut chewing. Our study result showed that MetS was a risk factor for OPMD. In addition, a recent study also revealed that sweet beverage consumption elevated risk of overall cancer and breast cancer [43]. The promotion of a MetS prevention programme after controlling for sugar-sweetened beverage or diet might reduce OPMD and oral cancer incidence in the future.

Several limitations existed in our study. First, several confounding factors that may link MetS and oral cancer, such as family history of oral cancer and history of chronic diseases other than MetS, were not considered. Second, the results of our study were derived from Taiwanese individuals older than 30 years, so external generalization of our results to other regions would be limited especially on the grounds of ethnic, genetic and dietary backgrounds. Third, the association between MetS and verrucous hyperplasia, erythroplakia, and erythroleukoplakia should be interpreted with great caution given the limited number of cases in our population. Fourth, possible information bias exists for self-reported variables, especially oral habits. Betel nut chewing, smoking, and alcohol drinking are behaviours that are deviant from social norms and regulations and can be possibly under-reported. Evidence on this phenomena has been demonstrated for reporting smoking behaviour [44, 45]. This notion might explain the 38 OSF subjects who reported never betel quid chewing, which contradicts the well-known association between OSF and betel quid chewing.

In conclusion, our prospective cohort study design affirmed the notion that MetS elevated the risk of OPMD. This epidemiological evidence provides new insight for health policy makers to promote MetS prevention to reduce OPMD and oral cancer in the future.

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Figure Legend

Figure 1 Flow chart for prospective normal cohort study design

Table 1 The incidence (per 1,000) of oral potentially malignant disorders by demographic features, status of metabolic syndrome and other associated risk factors

			OPMD		OSF		Leukoplakia		Verrucous hyperplasia		Erythroplakia+ Erythroleukoplakia	
	N	Person years	No.	‰	No.	‰	No.	‰	No.	‰	No.	‰
Overall	17,590	116732.06	716	6.13	149	1.28	521	4.46	20	0.17	26	0.22
Metabolic Syndrome												
Yes	5,789	38416.38	295	7.68	58	1.51	219	5.70	7	0.18	11	0.29
No	11,801	78315.68	421	5.38	91	1.16	302	3.86	13	0.17	15	0.19
Age												
30-39	1,178	8296.07	47	5.67	13	1.57	28	3.38	1	0.12	5	0.60
40-49	4,359	29193.98	210	7.19	42	1.44	154	5.28	8	0.27	6	0.21
50-59	5,538	35137.59	267	7.60	48	1.37	205	5.83	6	0.17	8	0.23
60-69	4,176	27778.33	160	5.76	37	1.33	115	4.14	4	0.14	4	0.14
70+	2,339	16326.09	32	1.96	9	0.55	19	1.16	1	0.06	3	0.18
Sex												
Male	15,619	104569.65	703	6.72	146	1.40	511	4.89	20	0.19	26	0.25
Female	1,971	12162.41	13	1.07	3	0.25	10	0.82	0	0.00	0	0.00
Education												
University	2140	13691.15	53	3.87	4	0.29	47	3.43	1	0.07	1	0.07
Senior high school	4173	26814.93	174	6.49	39	1.45	126	4.70	3	0.11	6	0.22
Junior high school or lower	11228	75877.21	487	6.42	106	1.40	347	4.57	16	0.21	18	0.24
Betel quid chewing												
Never	11,925	79006.46	256	3.24	38	0.48	203	2.57	10	0.13	5	0.06
Quit*	3,544	23719.97	236	9.95	62	2.61	162	6.83	6	0.25	6	0.25
Current	2,110	13920.02	224	16.09	49	3.52	156	11.21	4	0.29	15	1.08
Smoking												
Never	6,976	46286.91	101	2.18	21	0.45	75	1.62	1	0.02	4	0.09
Quit*	3,656	24678.95	126	5.11	36	1.46	82	3.32	3	0.12	5	0.20
Current	6,947	45680.37	489	10.70	92	2.01	364	7.97	16	0.35	17	0.37

Alcohol drinking												
Never	8,041	53484.46	212	3.96	48	0.90	155	2.90	4	0.07	5	0.09
Quit*	1,009	6798.76	58	8.53	10	1.47	44	6.47	2	0.29	2	0.29
Current	8,529	56365.96	446	7.91	91	1.61	322	5.71	14	0.25	19	0.34
BMI (kg/m²)												
<18.5	422	2852.29	9	3.16	5	1.75	3	1.05	0	0.00	1	0.35
18.5-24.9	8,844	58824.11	313	5.32	66	1.12	221	3.76	13	0.22	13	0.22
>25	8,324	55055.66	394	7.16	78	1.42	297	5.39	7	0.13	12	0.22
Triglyceride (mg/dl)												
<150	12,178	81399.38	405	4.98	87	1.07	289	3.55	14	0.17	15	0.18
≥150	5,412	35332.68	311	8.80	62	1.75	232	6.57	6	0.17	11	0.31
HDL-C (mg/dl) **												
Abnormal	5,684	37372.54	268	7.17	50	1.34	204	5.46	5	0.13	9	0.24
Normal	11,781	78407.84	441	5.62	98	1.25	312	3.98	14	0.18	17	0.22
Blood pressure (mm/Hg)***												
Normal	10,869	71713.89	440	6.14	94	1.31	321	4.48	12	0.17	13	0.18
Elevated risk	2,858	19152.31	127	6.63	23	1.20	91	4.75	7	0.37	6	0.31
Hypertension	3,863	25865.86	149	5.76	32	1.24	109	4.21	1	0.04	7	0.27
Glucose (mg/dl)												
<100	11,974	78755.06	454	5.76	90	1.14	332	4.22	13	0.17	19	0.24
100-125	3,907	26462.49	165	6.24	37	1.40	120	4.53	5	0.19	3	0.11
>125	1,709	11514.51	97	8.42	22	1.91	69	5.99	2	0.17	4	0.35
Meat												
Seldom	4,820	31984.38	171	5.35	38	1.19	127	3.97	3	0.09	3	0.09
Infrequent	11,904	78845.33	488	6.19	94	1.19	360	4.57	13	0.16	21	0.27
Frequent	829	5625.25	56	9.96	17	3.02	33	5.87	4	0.71	2	0.36
Vegetable												
Seldom	3,679	24216.53	172	7.10	42	1.73	124	5.12	1	0.04	5	0.21
Infrequent	13,469	89529.87	527	5.89	105	1.17	384	4.29	19	0.21	19	0.21
Frequent	308	2045.50	6	2.93	0	0.00	6	2.93	0	0.00	0	0.00

Fruit												
Seldom	1,608	10685.41	102	9.55	20	1.87	75	7.02	2	0.19	5	0.47
Infrequent	7,190	47575.85	333	7.00	74	1.56	233	4.90	10	0.21	16	0.34
Frequent	8,773	58318.08	280	4.80	55	0.94	212	3.64	8	0.14	5	0.09

OSF: oral submucosa fibrosis; ***Quit**: Quit betel quid chewing, quit smoking or quit alcohol drinking defined as those who once participated in these oral habits but no longer participate in these habit on the day of interview.

****HDL-C:** Abnormal defined as (male with 0<HDL<40) or (female with 0<HDL<50). Normal defined as (male with 40 ≤ HDL) or (female with 50 ≤ HDL)

*****Hypertension**: Normal defined as systolic blood pressure (sbp)<130 or diastolic blood pressure (dbp)<85. Elevated risk defined as 130 ≤ sbp<140 or 85 ≤ dbp<90. Hypertension defined as sbp≥140 or dbp≥90.

Table 2 The association between MetS, other factors and oral potentially malignant disorders (MetS → OPMD)

	RR	95% CI		aRR	95% CI	
Metabolic syndrome						
Yes vs No	1.42	1.22	1.66	1.33	1.14	1.55
Sex						
Male vs Female	7.14	3.94	12.94	3.49	1.89	6.44
Age groups (vs 70+)						
30-39	2.89	1.85	4.52	2.17	1.35	3.47
40-49	3.53	2.43	5.12	2.63	1.79	3.85
50-59	3.63	2.52	5.24	3.10	2.14	4.49
60-69	2.85	1.95	4.16	2.53	1.73	3.71
Betel nut chewing (vs Never)						
Quit*	3.03	2.54	3.63	2.00	1.62	2.47
Current	4.92	4.10	5.89	2.68	2.16	3.33
Cigarette smoking (vs Never)						
Quit*	2.32	1.78	3.03	1.31	0.96	1.78
Current	4.90	3.94	6.09	2.47	1.90	3.20
Alcohol drinking (vs Never)						
Quit*	2.18	1.62	2.92	1.23	0.90	1.68
Current	1.95	1.65	2.30	1.03	0.86	1.23
Meat (vs Seldom)						
Infrequent	1.13	0.95	1.35	0.95	0.79	1.13
Frequent	1.77	1.30	2.41	1.23	0.90	1.68
Vegetable (vs Seldom)						
Infrequent	0.83	0.70	0.99	0.92	0.77	1.10
Frequent	0.36	0.15	0.87	0.46	0.19	1.11
Fruit (vs Seldom)						
Infrequent	0.74	0.59	0.93	0.91	0.72	1.15
Frequent	0.51	0.40	0.64	0.79	0.62	1.00
Education level (vs Junior high school or lower)						
Senior high school	1.00	0.84	1.19	0.97	0.80	1.17
University	0.60	0.45	0.81	0.84	0.62	1.14

aRR: adjusted rate ratio; **CI**: confidence interval; ***Quit:** quit betel quid chewing, quit smoking or quit alcohol drinking defined as those who once participated in these oral habits but no longer participate in these habits on the day of interview.

Table 3 The effect of metabolic syndrome components on oral potentially malignant disorders

	All OPMD			
	aRR*	**95% CI**		**p-value**
Component of metabolic syndrome				
Central obesity	1.22	1.04	1.44	0.0162
Hypertriglyceridaemia	1.26	1.07	1.49	0.0066
Low HDL-C	1.12	0.95	1.32	0.1851
Elevated blood pressure	0.93	0.79	1.09	0.3586
Hyperglycaemia	1.20	1.02	1.41	0.0297
Metabolic syndrome score	1.14	1.08	1.20	< 0.0001

aRR: adjusted rate ratio; **CI**: confidence interval.

* Adjusted rate ratio for components of metabolic syndrome and metabolic syndrome score were treated in different models with adjustment of age, sex, education level, betel nut chewing, cigarette smoking, alcohol drinking, meat, vegetable and fruit consumption.

Table 4 The association between metabolic syndrome and sub-types of oral potentially malignant disorders using multi-variable Poisson regression

	Leukoplakia			OSF			Verrucous hyperplasia			Erythroplakia + Erythroleukoplakia		
	aRR*	95% CI		aRR**	95% CI		aRR***	95% CI		aRR***	95% CI	
Metabolic syndrome												
Yes vs No	1.37	1.14	1.64	1.22	0.87	1.71	1.33	0.51	3.46	1.59	0.67	3.75
Component of metabolic syndrome												
Central obesity	1.30	1.07	1.57	1.06	0.74	1.52	1.17	0.47	2.89	0.94	0.37	2.36
Hypertriglyceridaemia	1.29	1.06	1.57	1.21	0.83	1.76	0.98	0.40	2.40	1.39	0.54	3.58
Low HDL-C	1.17	0.97	1.42	0.94	0.64	1.38	0.79	0.31	1.99	1.18	0.47	2.97
Elevated blood pressure	0.90	0.75	1.09	0.95	0.66	1.37	1.34	0.46	3.85	1.22	0.50	3.00
Hyperglycaemia	1.16	0.96	1.41	1.43	0.99	2.05	1.28	0.52	3.19	0.99	0.37	2.64
Metabolic syndrome score	1.16	1.09	1.24	1.10	0.98	1.24	1.02	0.68	1.54	1.13	0.83	1.55

aRR: adjusted rate ratio; **CI**: confidence interval; **OSF**: oral submucous fibrosis

* Adjusted rate ratio for metabolic syndrome, components of metabolic syndrome, and metabolic syndrome score were treated in different models with adjustment of age, sex, education level, betel nut chewing, cigarette smoking, alcohol drinking, meat, vegetable and fruit consumption.

** Adjusted rate ratio for metabolic syndrome, components of metabolic syndrome, and metabolic syndrome score were treated in different models with adjustment of age, sex, education level, betel nut chewing, cigarette smoking, alcohol drinking, meat, and fruit consumption.

*** Adjusted rate ratio for metabolic syndrome, components of metabolic syndrome, and metabolic syndrome score were treated in different models with adjustment of betel nut chewing and cigarette smoking.

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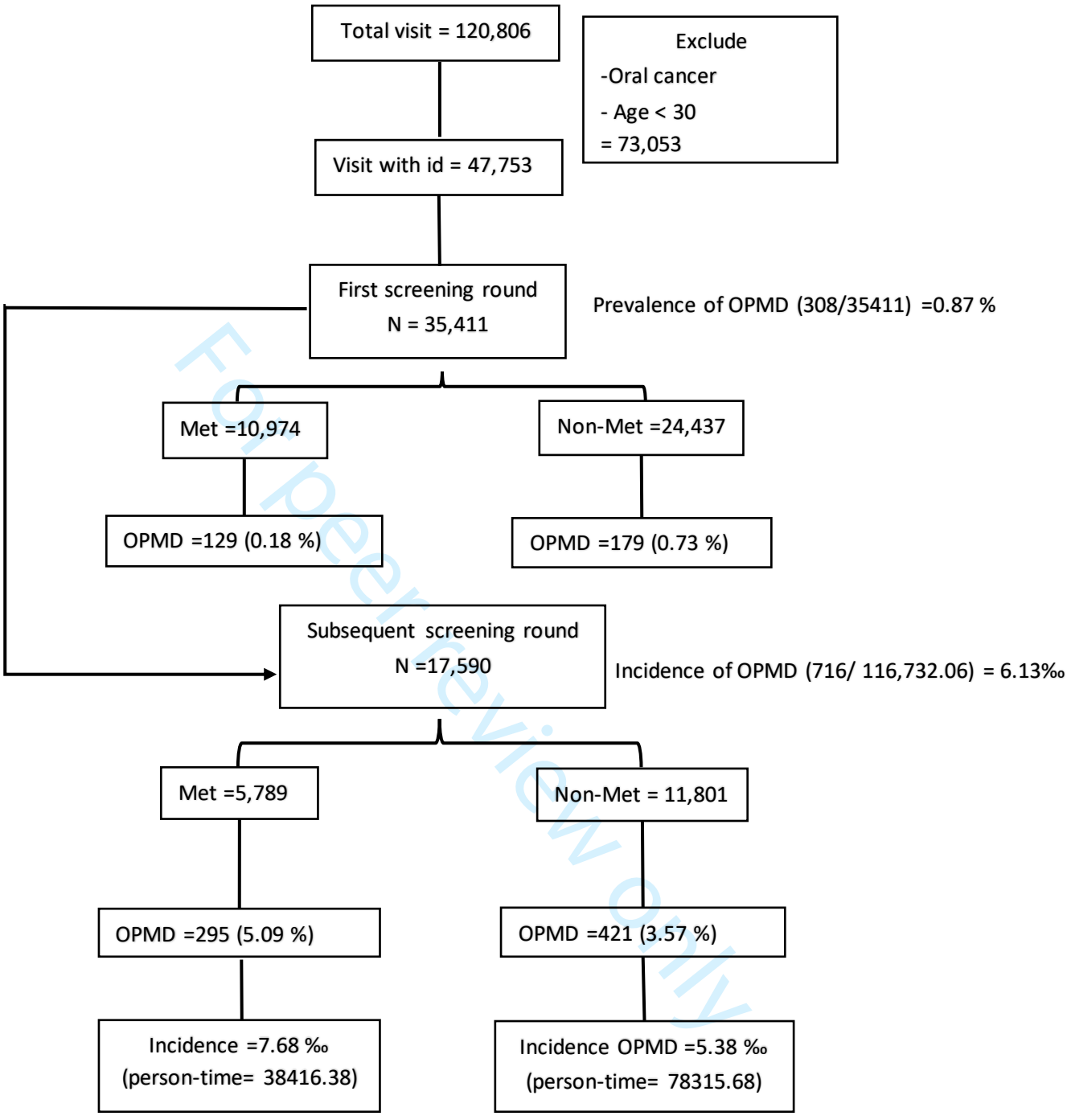

Figure 1 The flow chart for prospective normal cohort study design

Supplement Table 1 The association between MetS, other factors and prevalence of oral potentially malignant disorders

	OR	95%CI		aOR	95%CI	
Metabolic syndrome						
Yen vs No	1.61	1.28	2.02	1.44	1.14	1.82
Sex						
Male vs Female	7.32	4.65	11.53	2.50	1.50	4.16
Age groups (vs 70+)						
30-39	0.83	0.39	1.77	0.87	0.39	1.92
40-49	1.69	1.02	2.77	1.33	0.79	2.25
50-59	2.52	1.58	4.04	2.23	1.38	3.62
60-69	1.83	1.11	3.01	1.73	1.04	2.86
Betel nut chewing (vs Never)						
Quit*	3.33	2.53	4.37	1.40	1.04	1.90
Current	5.71	4.34	7.52	2.00	1.47	2.74
Cigarette smoking (vs Never)						
Quit*	4.72	3.23	6.91	2.66	1.72	4.12
Current	8.89	6.48	12.19	4.74	3.25	6.92
Alcohol drinking (vs Never)						
Quit*	2.49	1.95	3.16	0.98	0.59	1.63
Current	2.62	1.62	4.24	1.01	0.77	1.32
Meat (vs Seldom)						
Infrequent	1.28	0.98	1.67	1.00	0.76	1.32
Frequent	2.85	1.83	4.45	1.67	1.06	2.63
Vegetable (vs Seldom)						
Infrequent	0.82	0.63	1.07	0.88	0.68	1.16
Frequent	0.48	0.15	1.52	0.53	0.17	1.71
Fruit (vs Seldom)						
Infrequent	0.71	0.49	1.02	1.00	0.68	1.46
Frequent	0.54	0.38	0.78	1.02	0.69	1.50
Education level (vs Junior high school or lower)						
Senior high school	1.00	0.77	1.29	1.06	0.80	1.41
University	0.54	0.36	0.82	0.84	0.55	1.30

aOR: adjusted odds ratio; **CI**: confidence interval; ***Quit:** quit betel quid chewing, quit smoking or quit alcohol drinking defined as those who once participated in these oral habits but no longer participate in these habits on the day of interview.

Supplement Table 2 The association between Component of MetS, other factors and oral potentially malignant disorders (MetS → OPMD)

	RR	95% CI		aRR	95% CI	
Component of metabolic syndrome						
Central obesity	1.36	1.17	1.58	1.22	1.04	1.44
Hypertriglyceridaemia	1.78	1.53	2.07	1.26	1.07	1.49
Low HDL-C	1.26	1.08	1.47	1.12	0.95	1.32
Elevated blood pressure	1.00	0.86	1.17	0.93	0.79	1.09
Hyperglycaemia	1.21	1.04	1.42	1.20	1.02	1.41
Sex						
Male vs Female	7.14	3.94	12.94	3.57	1.94	6.59
Age groups (vs 70+)						
30-39	2.89	1.85	4.52	2.19	1.34	3.56
40-49	3.53	2.43	5.12	2.65	1.78	3.94
50-59	3.63	2.52	5.24	3.12	2.13	4.58
60-69	2.85	1.95	4.16	2.56	1.73	3.79
Betel nut chewing (vs Never)						
Quit*	3.03	2.54	3.63	1.94	1.57	2.40
Current	4.92	4.10	5.89	2.59	2.08	3.22
Cigarette smoking (vs Never)						
Quit*	2.32	1.78	3.03	1.32	0.96	1.79
Current	4.90	3.94	6.09	2.42	1.86	3.14
Alcohol drinking (vs Never)						
Quit*	2.18	1.62	2.92	1.24	0.90	1.70
Current	1.95	1.65	2.30	1.03	0.86	1.24
Meat (vs Seldom)						
Infrequent	1.13	0.95	1.35	0.94	0.79	1.13
Frequent	1.77	1.30	2.41	1.22	0.90	1.67
Vegetable (vs Seldom)						
Infrequent	0.83	0.70	0.99	0.93	0.78	1.12
Frequent	0.36	0.15	0.87	0.48	0.20	1.14
Fruit (vs Seldom)						
Infrequent	0.74	0.59	0.93	0.91	0.72	1.15
Frequent	0.51	0.40	0.64	0.77	0.60	0.98
Education level (vs Junior high school or lower)						
Senior high school	1.00	0.84	1.19	0.98	0.81	1.19
University	0.60	0.45	0.81	0.84	0.62	1.14

aRR: adjusted rate ratio; **CI**: confidence interval; ***Quit**: quit betel quid chewing, quit smoking or quit alcohol drinking defined as those who once participated in these oral habits but no longer participate in these habits on the day of interview.

Supplement Table 3 The association between MetS score, other factors and oral potentially malignant disorders (MetS → OPMD)

	RR	95%CI		aRR	95%CI	
Metabolic syndrome						
Score	1.18	1.12	1.24	1.14	1.08	1.20
Sex						
Male vs Female	7.14	3.94	12.94	3.51	1.90	6.47
Age groups (vs 70+)						
30-39	2.89	1.85	4.52	2.18	1.36	3.50
40-49	3.53	2.43	5.12	2.64	1.80	3.87
50-59	3.63	2.52	5.24	3.09	2.13	4.48
60-69	2.85	1.95	4.16	2.53	1.73	3.70
Betel nut chewing (vs Never)						
Quit*	3.03	2.54	3.63	1.98	1.61	2.44
Current	4.92	4.10	5.89	2.63	2.12	3.27
Cigarette smoking (vs Never)						
Quit*	2.32	1.78	3.03	1.31	0.96	1.79
Current	4.90	3.94	6.09	2.48	1.91	3.22
Alcohol drinking (vs Never)						
Quit*	2.18	1.62	2.92	1.23	0.90	1.68
Current	1.95	1.65	2.30	1.03	0.86	1.23
Meat (vs Seldom)						
Infrequent	1.13	0.95	1.35	0.95	0.79	1.14
Frequent	1.77	1.30	2.41	1.23	0.90	1.68
Vegetable (vs Seldom)						
Infrequent	0.83	0.70	0.99	0.92	0.77	1.10
Frequent	0.36	0.15	0.87	0.46	0.19	1.11
Fruit (vs Seldom)						
Infrequent	0.74	0.59	0.93	0.92	0.73	1.15
Frequent	0.51	0.40	0.64	0.79	0.62	1.01
Education level (vs Junior high school or lower)						
Senior high school	1.00	0.84	1.19	0.97	0.81	1.17
University	0.60	0.45	0.81	0.84	0.62	1.14

aRR: adjusted rate ratio; **CI**: confidence interval; ***Quit**: quit betel quid chewing, quit smoking or quit alcohol drinking defined as those who once participated in these oral habits but no longer participate in these habits on the day of interview.

Supplement Table 4 The association between MetS, other factors and oral submucous fibrosis (MetS → OSF)

	RR	95%CI		aRR	95%CI	
Metabolic syndrome						
Yen vs No	1.35	0.96	1.90	1.22	0.87	1.71
Sex						
Male vs Female	8.16	2.02	32.94	3.34	0.78	14.26
Age groups (vs 70+**)**						
30-39	2.88	1.23	6.73	2.61	1.04	6.54
40-49	2.60	1.26	5.34	2.08	0.97	4.47
50-59	2.22	1.08	4.56	1.99	0.96	4.13
60-69	2.25	1.08	4.69	2.07	0.99	4.33
Betel nut chewing (vs Never)						
Quit*	5.31	3.49	8.06	3.71	2.23	6.16
Current	7.82	5.07	12.05	4.77	2.87	7.92
Cigarette smoking (vs Never)						
Quit*	3.58	2.03	6.34	1.60	0.77	3.32
Current	5.10	3.07	8.47	1.96	1.04	3.66
Alcohol drinking (vs Never)						
Quit*	1.78	0.90	3.53	0.72	0.35	1.47
Current	1.80	1.25	2.59	0.83	0.56	1.23
Meat (vs Seldom)						
Infrequent	1.03	0.69	1.52	0.84	0.56	1.24
Frequent	2.65	1.47	4.77	1.71	0.94	3.11
Fruit (vs Seldom)						
Infrequent	0.92	0.54	1.56	1.11	0.65	1.91
Frequent	0.55	0.32	0.95	0.87	0.50	1.51
Education level (vs Junior high school or lower)						
Senior high school	1.11	0.76	1.61	1.07	0.70	1.62
University	0.23	0.08	0.62	0.33	0.12	0.94

aRR: adjusted rate ratio; **CI**: confidence interval ***Quit**: quit betel quid chewing, quit smoking or quit alcohol drinking defined as those who once participated in these oral habits but no longer participate in these habits on the day of interview.

Supplement Table 5 The association between Component of MetS, other factors and oral submucous fibrosis (MetS → OSF)

	RR	95%CI		aRR	95%CI	
Component of metabolic syndrome						
Central obesity	1.21	0.87	1.70	1.06	0.74	1.52
Hypertriglyceridaemia	1.67	1.19	2.34	1.21	0.83	1.76
Low HDL-C	1.06	0.74	1.50	0.94	0.64	1.38
Elevated blood pressure	1.04	0.74	1.47	0.95	0.66	1.37
Hyperglycaemia	1.37	0.97	1.92	1.43	0.99	2.05
Sex						
Male vs Female	8.16	2.02	32.94	3.27	0.77	13.93
Age groups (vs 70+**)**						
30-39	2.88	1.23	6.73	2.60	1.02	6.63
40-49	2.60	1.26	5.34	2.05	0.95	4.43
50-59	2.22	1.08	4.56	1.89	0.91	3.91
60-69	2.25	1.08	4.69	2.03	0.97	4.26
Betel nut chewing (vs Never)						
Quit*	5.31	3.49	8.06	3.77	2.26	6.31
Current	7.82	5.07	12.05	4.88	2.92	8.14
Cigarette smoking (vs Never)						
Quit*	3.58	2.03	6.34	1.59	0.77	3.29
Current	5.10	3.07	8.47	1.91	1.02	3.59
Alcohol drinking (vs Never)						
Quit*	1.78	0.90	3.53	0.73	0.36	1.50
Current	1.80	1.25	2.59	0.84	0.56	1.25
Meat (vs Seldom)						
Infrequent	1.03	0.69	1.52	0.82	0.55	1.21
Frequent	2.65	1.47	4.77	1.67	0.91	3.09
Fruit (vs Seldom)						
Infrequent	0.92	0.54	1.56	1.12	0.65	1.92
Frequent	0.55	0.32	0.95	0.85	0.49	1.48
Education level (vs Junior high school or lower)						
Senior high school	1.11	0.76	1.61	1.09	0.71	1.66
University	0.23	0.08	0.62	0.34	0.12	0.95

aRR: adjusted rate ratio; **CI**: confidence interval; ***Quit**: quit betel quid chewing, quit smoking or quit alcohol drinking defined as those who once participated in these oral habits but no longer participate in these habits on the day of interview.

Supplement Table 6 The association between MetS score, other factors and oral submucous fibrosis (MetS → OSF)

	RR	95%CI		aRR	95%CI	
Metabolic syndrome						
Score	1.15	1.03	1.30	1.10	0.98	1.24
Sex						
Male vs Female	8.16	2.02	32.94	3.37	0.79	14.38
Age groups (vs 70+)						
30-39	2.88	1.23	6.73	2.63	1.05	6.62
40-49	2.60	1.26	5.34	2.10	0.98	4.50
50-59	2.22	1.08	4.56	1.99	0.96	4.12
60-69	2.25	1.08	4.69	2.07	0.99	4.33
Betel nut chewing (vs Never)						
Quit*	5.31	3.49	8.06	3.68	2.21	6.11
Current	7.82	5.07	12.05	4.70	2.83	7.80
Cigarette smoking (vs Never)						
Quit*	3.58	2.03	6.34	1.60	0.77	3.33
Current	5.10	3.07	8.47	1.96	1.05	3.67
Alcohol drinking (vs Never)						
Quit*	1.78	0.90	3.53	0.72	0.35	1.47
Current	1.80	1.25	2.59	0.83	0.56	1.23
Meat (vs Seldom)						
Infrequent	1.03	0.69	1.52	0.84	0.57	1.24
Frequent	2.65	1.47	4.77	1.71	0.94	3.11
Fruit (vs Seldom)						
Infrequent	0.92	0.54	1.56	1.12	0.65	1.92
Frequent	0.55	0.32	0.95	0.87	0.50	1.51
Education level (vs Junior high school or lower)						
Senior high school	1.11	0.76	1.61	1.07	0.70	1.63
University	0.23	0.08	0.62	0.33	0.12	0.94

aRR: adjusted rate ratio; **CI**: confidence interval; ***Quit**: quit betel quid chewing, quit smoking or quit alcohol drinking defined as those who once participated in these oral habits but no longer participate in these habits on the day of interview.

Supplement Table 7 The association between MetS, other factors and Leukoplakia (MetS → Leukoplakia)

	RR	95%CI		aRR	95%CI	
Metabolic syndrome						
Yen vs No	1.45	1.22	1.73	1.37	1.14	1.64
Sex						
Male vs Female	6.48	3.36	12.52	3.29	1.67	6.48
Age groups (vs 70+)						
30-39	2.92	1.63	5.22	2.08	1.13	3.81
40-49	4.38	2.72	7.05	3.20	1.97	5.18
50-59	4.86	3.04	7.78	4.09	2.55	6.57
60-69	3.51	2.16	5.71	3.13	1.92	5.09
Betel nut chewing (vs Never)						
Quit*	2.70	2.20	3.33	1.81	1.42	2.30
Current	4.45	3.61	5.49	2.42	1.88	3.12
Cigarette smoking (vs Never)						
Quit*	2.04	1.49	2.80	1.22	0.86	1.74
Current	4.88	3.80	6.27	2.66	1.98	3.58
Alcohol drinking (vs Never)						
Quit*	2.29	1.63	3.20	1.36	0.95	1.96
Current	1.95	1.61	2.36	1.06	0.86	1.31
Meat (vs Seldom)						
Infrequent	1.12	0.91	1.37	0.93	0.76	1.15
Frequent	1.47	1.00	2.16	1.01	0.68	1.51
Vegetable (vs Seldom)						
Infrequent	0.84	0.69	1.03	0.93	0.75	1.14
Frequent	0.49	0.20	1.19	0.60	0.25	1.45
Fruit (vs Seldom)						
Infrequent	0.68	0.53	0.89	0.85	0.65	1.11
Frequent	0.51	0.39	0.66	0.78	0.59	1.03
Education level (vs Junior high school or lower)						
Senior high school	0.99	0.80	1.22	0.98	0.78	1.22
University	0.74	0.55	1.01	1.03	0.74	1.43

aRR: adjusted rate ratio; **CI**: confidence interval; ***Quit**: quit betel quid chewing, quit smoking or quit alcohol drinking defined as those who once participated in these oral habits but no longer participate in these habits on the day of interview.

Supplement Table 8 The association between Component of MetS, other factors and Leukoplakia (MetS → Leukoplakia)

	RR	95%CI		aRR	95%CI	
Component of metabolic syndrome						
Central obesity	1.43	1.20	1.70	1.30	1.07	1.57
Hypertriglyceridaemia	1.85	1.56	2.21	1.29	1.06	1.57
Low HDL-C	1.34	1.12	1.60	1.17	0.97	1.42
Elevated blood pressure	0.99	0.83	1.18	0.90	0.75	1.09
Hyperglycaemia	1.20	1.00	1.44	1.16	0.96	1.41
Sex						
Male vs Female	6.48	3.36	12.52	3.43	1.74	6.75
Age groups (vs 70+)						
30-39	2.92	1.63	5.22	2.15	1.14	4.06
40-49	4.38	2.72	7.05	3.34	2.00	5.57
50-59	4.86	3.04	7.78	4.30	2.61	7.08
60-69	3.51	2.16	5.71	3.29	1.97	5.49
Betel nut chewing (vs Never)						
Quit*	2.70	2.20	3.33	1.73	1.36	2.20
Current	4.45	3.61	5.49	2.31	1.79	2.98
Cigarette smoking (vs Never)						
Quit*	2.04	1.49	2.80	1.23	0.86	1.75
Current	4.88	3.80	6.27	2.60	1.93	3.50
Alcohol drinking (vs Never)						
Quit*	2.29	1.63	3.20	1.37	0.95	1.98
Current	1.95	1.61	2.36	1.06	0.86	1.32
Meat (vs Seldom)						
Infrequent	1.12	0.91	1.37	0.94	0.76	1.16
Frequent	1.47	1.00	2.16	1.02	0.68	1.51
Vegetable (vs Seldom)						
Infrequent	0.84	0.69	1.03	0.92	0.75	1.14
Frequent	0.49	0.20	1.19	0.60	0.25	1.45
Fruit (vs Seldom)						
Infrequent	0.68	0.53	0.89	0.85	0.65	1.11
Frequent	0.51	0.39	0.66	0.78	0.59	1.03
Education level (vs Junior high school or lower)						
Senior high school	0.99	0.80	1.22	0.98	0.78	1.22
University	0.74	0.55	1.01	1.04	0.75	1.44

aRR: adjusted rate ratio; **CI**: confidence interval; ***Quit**: quit betel quid chewing, quit smoking or quit alcohol drinking defined as those who once participated in these oral habits but no longer participate in these habits on the day of interview.

Supplement Table 9 The association between MetS score, other factors and Leukoplakia (MetS → Leukoplakia)

	RR	95%CI		aRR	95%CI	
Metabolic syndrome						
Score	1.20	1.13	1.27	1.16	1.09	1.24
Sex						
Male vs Female	6.48	3.36	12.52	3.31	1.68	6.51
Age groups (vs 70+)						
30-39	2.92	1.63	5.22	2.09	1.14	3.84
40-49	4.38	2.72	7.05	3.22	1.99	5.22
50-59	4.86	3.04	7.78	4.08	2.54	6.54
60-69	3.51	2.16	5.71	3.12	1.92	5.08
Betel nut chewing (vs Never)						
Quit*	2.70	2.20	3.33	1.79	1.40	2.27
Current	4.45	3.61	5.49	2.37	1.84	3.05
Cigarette smoking (vs Never)						
Quit*	2.04	1.49	2.80	1.22	0.86	1.74
Current	4.88	3.80	6.27	2.68	1.99	3.60
Alcohol drinking (vs Never)						
Quit*	2.29	1.63	3.20	1.37	0.95	1.97
Current	1.95	1.61	2.36	1.05	0.85	1.30
Meat (vs Seldom)						
Infrequent	1.12	0.91	1.37	0.94	0.76	1.16
Frequent	1.47	1.00	2.16	1.02	0.68	1.51
Vegetable (vs Seldom)						
Infrequent	0.84	0.69	1.03	0.92	0.75	1.14
Frequent	0.49	0.20	1.19	0.60	0.25	1.45
Fruit (vs Seldom)						
Infrequent	0.68	0.53	0.89	0.85	0.65	1.11
Frequent	0.51	0.39	0.66	0.78	0.59	1.03
Education level (vs Junior high school or lower)						
Senior high school	0.99	0.80	1.22	0.98	0.78	1.22
University	0.74	0.55	1.01	1.04	0.75	1.44

aRR: adjusted rate ratio; **CI**: confidence interval; ***Quit**: quit betel quid chewing, quit smoking or quit alcohol drinking defined as those who once participated in these oral habits but no longer participate in these habits on the day of interview.

Supplement Table 10 The association between MetS, other factors and Verrucous hyperplasia (MetS → Verrucous hyperplasia)

	RR	95%CI		aRR	95%CI	
Metabolic syndrome						
Yen vs No	1.32	0.51	3.40	1.33	0.51	3.46
Betel nut chewing (vs Never)						
Quit*	1.92	0.64	5.71	1.24	0.40	3.82
Current	2.71	0.84	8.81	1.13	0.34	3.74
Cigarette smoking (vs Never)						
Quit*	1.91	0.12	30.49	1.72	0.09	31.37
Current	17.03	2.26	128.38	15.80	2.04	122.28

aRR: adjusted rate ratio; **CI**: confidence interval; ***Quit**: quit betel quid chewing, quit smoking or quit alcohol drinking defined as those who once participated in these oral habits but no longer participate in these habits on the day of interview.

Supplement Table 11 The association between Component of MetS, other factors and Verrucous hyperplasia (MetS → Verrucous hyperplasia)

	RR	95%CI		aRR	95%CI	
Component of metabolic syndrome						
Central obesity	1.05	0.41	2.71	1.17	0.47	2.89
Hypertriglyceridaemia	1.26	0.47	3.42	0.98	0.40	2.40
Low HDL-C	0.88	0.31	2.50	0.79	0.31	1.99
Elevated blood pressure	1.04	0.40	2.69	1.34	0.46	3.85
Hyperglycaemia	1.13	0.42	3.05	1.28	0.52	3.19
Betel nut chewing (vs Never)						
Quit*	1.92	0.64	5.71	1.22	0.39	3.80
Current	2.71	0.84	8.81	0.84	0.23	3.13
Cigarette smoking (vs Never)						
Quit*	1.91	0.12	30.49	1.72	0.09	31.29
Current	17.03	2.26	128.38	16.34	2.00	133.78

aRR: adjusted rate ratio; **CI**: confidence interval; ***Quit**: quit betel quid chewing, quit smoking or quit alcohol drinking defined as those who once participated in these oral habits but no longer participate in these habits on the day of interview.

Supplement Table 12 The association between MetS score, other factors and Verrucous hyperplasia (MetS → Verrucous hyperplasia)

	RR	95%CI		aRR	95%CI	
Metabolic syndrome						
Score	1.01	0.67	1.54	1.02	0.68	1.54
Betel nut chewing (vs Never)						
Quit*	1.92	0.64	5.71	1.24	0.40	3.85
Current	2.71	0.84	8.81	1.15	0.34	3.91
Cigarette smoking (vs Never)						
Quit*	1.91	0.12	30.49	1.73	0.09	31.58
Current	17.03	2.26	128.38	15.73	2.01	122.98

aRR: adjusted rate ratio; **CI**: confidence interval; ***Quit**: quit betel quid chewing, quit smoking or quit alcohol drinking defined as those who once participated in these oral habits but no longer participate in these habits on the day of interview.

Supplement Table 13 The association between MetS, other factors and Erythroplakia + Erythroleukoplakia (MetS → Erythroplakia + Erythroleukoplakia)

	RR	95%CI		aRR	95%CI	
Metabolic syndrome						
Yen vs No	1.88	0.80	4.43	1.59	0.67	3.75
Betel nut chewing (vs Never)						
Quit*	4.31	1.16	16.03	4.47	0.93	21.46
Current	18.24	5.88	56.54	17.81	4.95	64.12
Cigarette smoking (vs Never)						
Quit*	1.91	0.48	7.62	0.84	0.15	4.60
Current	3.46	1.13	10.61	0.96	0.26	3.49

aRR: adjusted rate ratio; **CI**: confidence interval; ***Quit**: quit betel quid chewing, quit smoking or quit alcohol drinking defined as those who once participated in these oral habits but no longer participate in these habits on the day of interview.

Supplement Table 14 The association between Component of MetS, other factors and Erythroplakia + Erythroleukoplakia (MetS → Erythroplakia + Erythroleukoplakia)

	RR	95%CI		aRR	95%CI	
Component of metabolic syndrome						
Central obesity	1.24	0.52	2.94	0.94	0.37	2.36
Hypertriglyceridaemia	2.10	0.89	4.95	1.39	0.54	3.58
Low HDL-C	1.30	0.54	3.13	1.18	0.47	2.97
Elevated blood pressure	1.33	0.54	3.29	1.22	0.50	3.00
Hyperglycaemia	1.03	0.42	2.56	0.99	0.37	2.64
Betel nut chewing (vs Never)						
Quit*	4.31	1.16	16.03	4.49	0.94	21.55
Current	18.24	5.88	56.54	17.86	5.10	62.54
Cigarette smoking (vs Never)						
Quit*	1.91	0.48	7.62	0.85	0.15	4.65
Current	3.46	1.13	10.61	0.91	0.24	3.50

aRR: adjusted rate ratio; **CI**: confidence interval; ***Quit**: quit betel quid chewing, quit smoking or quit alcohol drinking defined as those who once participated in these oral habits but no longer participate in these habits on the day of interview.

Supplement Table 15 The association between MetS score, other factors and Erythroplakia + Erythroleukoplakia (MetS → Erythroplakia + Erythroleukoplakia)

	RR	95%CI		aRR	95%CI	
Metabolic syndrome						
Score	1.22	0.89	1.68	1.13	0.83	1.55
Betel nut chewing (vs Never)						
Quit*	4.31	1.16	16.03	4.49	0.94	21.54
Current	18.24	5.88	56.54	17.92	4.96	64.68
Cigarette smoking (vs Never)						
Quit*	1.91	0.48	7.62	0.84	0.15	4.60
Current	3.46	1.13	10.61	0.95	0.26	3.49

aRR: adjusted rate ratio; **CI**: confidence interval; ***Quit**: quit betel quid chewing, quit smoking or quit alcohol drinking defined as those who once participated in these oral habits but no longer participate in these habits on the day of interview.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Pages
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6,7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7,9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	10 (Figure)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted	10,11

		estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.