The Association between Ambient Fine Particulate Matter and Oral Neoplasm among Smokers and Betel Quids Chewers

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ABSTRACT

The association between fine particulate matter < 2.5 μm ($PM_{2.5}$) and oral neoplasm has barely been addressed. The purpose of this study is to elucidate the association between $PM_{2.5}$ and oral neoplasm, including oral potentially malignant disorder (OPMD) and oral cancer (OC), taking into account the geographical heterogeneity. Data for analysis were derived from nationwide OC screening program, targeting Taiwanese cigarette smokers and/or betel quid chewers, and the Taiwan Air Quality Monitoring Network between 2006 and 2016. Totally 3,864,045 smokers and/or betel quids chewers were enrolled in this study. Among them, 154,030 OPMD cases and 23,286 oral cancers were found during the study period. Information on age, gender, living area, personal oral habits, and monthly $PM_{2.5}$ concentration in average were collected. We used the Bayesian random-effect logistic regression model to assess the association between $PM_{2.5}$ and OPMD/OC. After adjusting for sex, age, and behavior of betel quid chewing and cigarette smoking, we found that subjects from areas of higher levels of $PM_{2.5}$ (≥ 35 μg m^{-3}) had an increased risk of OPMD/OC and OC by 11% (aRR = 1.11; 95% CI: 1.09–1.13) and 55% (aRR = 1.55; 95% CI: 1.49–1.60) respectively, compared to those from areas of lower $PM_{2.5}$ (< 35 μg m^{-3}). Such effect was further demonstrated in a concentration-dependent manner. Subjects from areas of higher $PM_{2.5}$ levels were found to have greater risk of OPMD/OC in Taiwan. Future studies are warranted to investigate the effect of personal $PM_{2.5}$ exposure on OPMD/OC risk.

Keywords: Particulate matter, Oral cancer, Nationwide screening program, Taiwan

1 INTRODUCTION

It is inevitable that air pollution has become environmental burden worldwide. Among all air pollutants, fine particulate matters (particulate matter with an aerodynamic diameter ≤ 2.5 μm; $PM_{2.5}$) are thought to be the most important toxicants in urban air (Kaiser 2005). In 2016, World Health Organization (WHO) reported that approximately 92% of the world's population were residing in places where level of the $PM_{2.5}$ exceeds WHO air quality guideline (AQG), an annual average concentration of 10 μg m^{-3} (WHO, 2006). Although studies have indicated a decreasing trend in $PM_{2.5}$ concentrations in many countries, $PM_{2.5}$ is still a significant public concern in Taiwan, due to many of the people in Taiwan still live in areas with the $PM_{2.5}$ exceeds 10 μg m^{-3} and the related adverse health effects such as cardiovascular disease, respiratory disease and cancers have been reported (Cheng and Hsu, 2019; Yang *et al.*, 2018).

Oral cancer (OC) is the fifth leading cause of cancer death and has been the fourth most common cancer in men for more than 10 consecutive years since 2003 in Taiwan (Ministry of Health and Welfare, 2018). In order to prevent the disease onset and to cure or slow the disease progression, the Taiwanese government has implemented the biennial nationwide OC screening focusing on
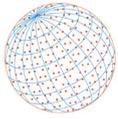
adults at a higher risk (betel quid chewers or smokers) since 2004 to detect oral potentially malignant disorder (OPMD) and OC (Chuang *et al.*, 2017). In addition, since betel quid chewing has been identified as a risk factor of OPMD and OC independently (Amarasinghe *et al.*, 2010; Ko *et al.*, 1995; Merchant *et al.*, 2000), and in conjunction with smoking and alcohol drinking (Yen *et al.*, 2007a, 2008; Yen *et al.*, 2008b), the Taiwanese government has reinforced the betel quid chewing prevention and control in recent decades. The betel quid chewing rate among male adults over 18 has been declined from 2007 to 2018 by 59.2% in Taiwan (Health Promotion Administration, 2019). Although age-standardized OC incidence rate increased continuously in both sexes before 2009, it has become flatten since then (Siewchaisakul *et al.*, 2020a).

The other risk factors of OPMD and OC include exposure to heavy metals (arsenic, nickel, and chromium) at high concentration (Chu *et al.*, 2019; Kaldor *et al.*, 1984; Su *et al.*, 2010; Yuan *et al.*, 2011), human papillomavirus (HPV) infection (Chaturvedi, 2012), presence of metabolic syndrome (MetS) (Yen *et al.*, 2011), and age younger than 70 years (Siewchaisakul *et al.*, 2020a).

Recent studies have shown that the level of $PM_{2.5}$ was associated with an increased risk in cardiovascular inflammatory marker such as C-reactive protein (CRP) in adults with MetS (Dabass *et al.*, 2018). Other inflammatory markers including T lymphocytes, macrophages, transforming growth factor (TGF)-β1, tumor necrosis factor (TNF)-α, and interleukin (IL)-6 were also found as underpinning the link between MetS and OPMD (Chiang *et al.*, 2002; Hsu *et al.*, 2014; Ujpál *et al.*, 2004). This led to the hypothesis that $PM_{2.5}$ may also associate with OPMD.

In 2013, $PM_{2.5}$ was noted by International Agency for Research on Cancer (IARC) as carcinogenic to human (Loomis *et al.*, 2013). Carcinomas that have been found to be associated with $PM_{2.5}$ are lung, leiomyoma, bladder cancer, and OC (Chu *et al.*, 2019; Hamra *et al.*, 2014; Mahalingaiah *et al.*, 2014). Previous study has revealed that the long-term $PM_{2.5}$ concentrations and daily mean concentrations over 35 μg m^{-3} varied by meteorological conditions and regions in Taiwan (Cheng and Hsu, 2019). Cheng and Hsu's (2019) study prompted us to determine the cut-off point of $PM_{2.5}$ and also take into account the heterogenous $PM_{2.5}$ exposure effect on OC between areas in current study. However, few population-based studies investigated the association between $PM_{2.5}$ and OC, especially OPMD.

We therefore aimed to elucidate the association between $PM_{2.5}$ and OPMD/OC, taking heterogeneity between areas into account based on the longitudinal data of air quality monitoring and nationwide OC screening in Taiwan.

2 METHODS

2.1 Study Population and Data Collection
2.1.1 Data source for oral neolplasm

A retrospective cohort design was conducted in this study. Population in this study was based on the nationwide OC screening program between 2006 and 2016. The program has been launched by Health Promotion Administration (HPA), Taiwan, since 2004. The details have been described by Chuang *et al.* (2017). The biennial OC screening program with visual inspection was done by the trained dentists and physicians and was targeting high risk population aged 30 years and above who had the habit of either cigarette smoking or betel quid chewing. Those with suspicious lesions would be invited by public health nurses to complete the confirmatory follow-up examination. We excluded those who had diagnosed with OC before screening and those cancer-free subjects who were diagnosed as epithelial dysplasia in oral cavity.

The definition of oral cancer was according to International Classification of Diseases, 9th Revision-Clinical Modification (codes 140–141, 143–146, and 148–149) and from the International Classification of Diseases, 10th Revision (codes C00–C06, C09–C10, C12–C14) including lip, tongue, gingival, floor of mouth, palate, other parts of mouth, oropharyngeal, hypopharyngeal and unspecified pharyngeal cancer. OPMD was defined when individuals were clinical diagnosed as leukoplakia, erythroleukoplakia, erythroplakia, oral submucous fibrosis, and verrucous hyperplasia.

Data on age at screening, sex, residential area (county/city), unhealthy oral habits (betel quid and cigarettes exposure) were retrieved. Subjects may attend the screening program multiple times. We kept only the latest record of subjects upon the detection of OPMD/OC at screening or before the clinical diagnosis of OC, or the last records of subjects who were free from OPMD/OC. The study
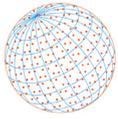
was approved by the Research Ethics Committee of National Taiwan University Hospital with informed consent pursuant to the regulations of the Institutional Review Board.

2.1.2 Exposure measurements of PM$_{2.5}$

Air quality data measured by Taiwan's Environmental Protection Administration (TEPA) were used to estimate PM$_{2.5}$ exposures. Since 1993, Taiwan Air Quality Monitoring Network (AQMN) has been established by TEPA to monitor nationwide air quality by 73 monitoring sites distributed in 22 cities/counties (TWEPA, 2019). The complete record of daily continuous monitoring of PM$_{2.5}$ were available since August, 2005. Daily PM$_{2.5}$ concentrations of all monitoring stations in AQMA from 2006 to 2016 were used for the whole year-round measurements and were grouped by city/county.

To investigate the association between PM$_{2.5}$ and OPMD/OC, these spatially averaged PM$_{2.5}$ data were chronically matched to study subjects' screening date by month and the city/county the subjects lived in to represent their PM$_{2.5}$ exposures.

2.2 Statistical Analysis

Descriptive information is reported as frequency and percentage. We first categorized the PM$_{2.5}$ concentration into dichotomous variable (low and high) using cut-off point of 35 μg m^{-3}, the third quartile of the monthly average PM$_{2.5}$ concentration of all the 22 cities/counties over eleven years. In addition to the dichotomous, we also categorized PM$_{2.5}$ by 10 μg m^{-3} into 5 groups (< 10, 10–19, 20–29, 30–39, and 40+ μg m^{-3}). The lowest PM$_{2.5}$ concentration group (< 10 μg m^{-3}) was used as the reference group.

Since PM$_{2.5}$ measurement was based on the level of county/city on monthly basis, we examined the associations between PM$_{2.5}$ and both OPMD/OC, OPMD or OC using the Bayesian univariable random-effects logistic regression models, treating county-specific PM$_{2.5}$ effects as random-effect variables. Age (30–49, 50–69, 70+), sex (male, female), and unhealthy oral habits (cigarette smoking only, betel quid chewing only and betel quid chewing and cigarette smoking) are the potential individual risk factors for oral cancer. We further conducted the multivariable analyses controlling the significant confounding factors based on the univariable model. Notably, we did model the PM$_{2.5}$ as dichotomous and polychotomous in different multivariable models. All tests assumed a two-sided type I error of 0.05 and were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC).

3 RESULTS AND DISCUSSION

There were 154,030 OPMD, 23,286 OC cases, and 3,686,729 subjects free from OPMD/OC included in the analyses. Frequency of demographic information and environmental risk exposure of betel quid, cigarette smoking is shown in Table 1. Most of the study population was diagnosed with OPMD in the age group of 30 to 49 years and with OC in the age group of 50 to 69 years. Men who had the habit of cigarette smoking and betel quid chewing were dominant in both OPMD and OC groups.

Fig. 1 shows the average concentrations of PM$_{2.5}$ by county/city in Taiwan. The highest average concentration was in Chiayi City with the mean of 34.05 μg m^{-3} (standard deviation [SD]: 14.52 μg m^{-3}). The lowest average concentration was in Taitung County with the mean of 11.82 μg m^{-3} (SD: 3.88 μg m^{-3}) (Table S1).

3.1 PM$_{2.5}$ and Risk of OPMD/OC

Fig. 2(a) shows the proportions of diagnosed OPMD and OC combined cases by county/city. The county/city with the highest proportion of diagnosed cases was Chiayi City (8.88%), the same city with the highest average PM$_{2.5}$ concentration, and the lowest proportion was in Taichung City (1.47%) (Table S2).

The effects of PM$_{2.5}$ and other related factors of OPMD/OC are elucidated in Table 2. In the crude univariable analysis, PM$_{2.5}$ with concentration 35 μg m^{-3} and above showed a significantly increased risk of OPMD/OC by 4% (RR = 1.04, 95% CI: 1.03–1.06) compared to concentration lower than 35 μg m^{-3}. In the multivariable analysis after adjusting for sex, age, betel quid chewing
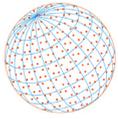
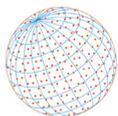**Table 1.** Frequency of demographic and risk factor for oral potentially malignant disorders or oral cancer.

	OPMD + OC				Only OPMD*				Only OC			
	Normal	(%)	Cases	(%)	Normal	(%)	Cases	(%)	Normal	(%)	Cases	(%)
PM$_{2.5}$ (µg m^{-3})												
< 10	107,378	2.9	4,710	2.7	107,378	2.9	4,238	2.8	107,378	2.9	472	2.0
10–19	1,224,835	33.2	55,677	31.4	1,224,835	33.2	50,065	32.5	1,224,835	33.2	5,612	24.1
20–29	1,501,073	40.7	71,242	40.2	1,501,073	40.7	62,009	40.3	1,501,073	40.7	9,233	39.7
30–39	601,697	16.3	30,343	17.1	601,697	16.3	25,413	16.5	601,697	16.3	4,930	21.2
≥ 40	251,746	6.8	15,344	8.7	251,746	6.8	12,305	8.0%	251,746	6.8	3,039	13.1
Sex												
Male	2,712,478	73.6	166,562	93.9	2,712,478	73.6	144,278	93.7	2,712,478	73.6	22,284	95.7
Female	974,251	26.4	10,754	6.1	974,251	26.4	9,752	6.3	974,251	26.4	1,002	4.3
Age (years)												
30–49	1,719,022	46.6	82,952	46.8	1,719,022	46.6	75,172	48.8	1,719,022	46.6	7,780	33.4
50–69	1,446,335	39.2	81,049	45.7	1,446,335	39.2	68,272	44.3	1,446,335	39.2	12,777	54.9
70+	521,372	14.1	13,315	7.5	521,372	14.1	10,586	6.9	521,372	14.1	2,729	11.7
Habit												
S	1,565,534	42.5	44166	24.9	1565534	42.5	39260	25.5	1565534	42.5	4906	21.1
B	347,703	9.4	8795	5.0	347703	9.4	7210	4.7	347703	9.4	1585	6.8
BS	1,773,492	48.1	124355	70.1	1773492	48.1	107560	69.8	1773492	48.1	16795	72.1

*(For OPMD the concentration was grouped in 5 groups from < 15 µg m^{-3} to ≥ 45 µg m^{-3} for only OPMD B: Betel quid chewing only; BS: Betel quid chewing and cigarette smoking; S: cigarette smoking only
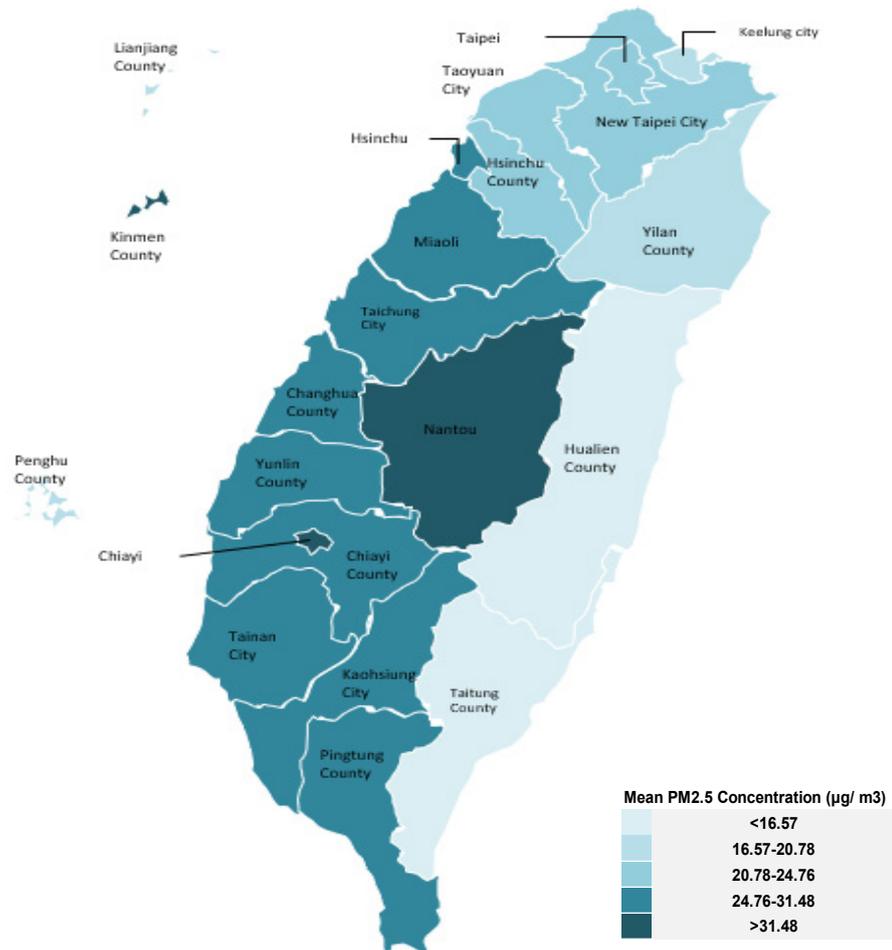
Fig. 1. Geographically gradients of monthly average PM$_{2.5}$ concentration by county/city. Quintile was used for classification of pattern.

Fig. 2. Geographically gradients of oral neoplasms by county/city. (a) rate (%) of OPMD and OC cases (b) rate (%) of OPMD cases (c) rate (%) of OC cases. Quintile was used for classification of pattern.

Table 2. Univariable and multivariable Bayesian random-effect logistic regression models for oral neoplasm (OPMD + OC).

Variables	RR	(95% CI)	aRR	(95% CI)
PM$_{2.5}$ (vs < 35 µg m^{-3})*				
≥ 35 µg m^{-3}	1.04	(1.03, 1.06)	1.11	(1.09, 1.13)
PM$_{2.5}$ (vs < 10 µg m^{-3})				
10–19 µg m^{-3}	1.10	(1.07, 1.14)	1.20	(1.16, 1.24)
20–29 µg m^{-3}	1.17	(1.13, 1.21)	1.36	(1.31, 1.40)
30–39 µg m^{-3}	1.16	(1.13, 1.20)	1.39	(1.34, 1.44)
≥ 40 µg m^{-3}	1.24	(1.19, 1.29)	1.52	(1.46, 1.57)
Sex (vs Female)				
Male	5.56	(5.46, 5.66)	4.81	(4.72, 4.91)
Age group (vs 70+, years)				
30–49	1.89	(1.85, 1.92)	1.99	(1.95, 2.02)
50–69	2.19	(2.15, 2.23)	2.29	(2.24, 2.33)
Habit (vs S)				
B	0.90	(0.88, 0.92)	1.23	(1.20, 1.26)
B + S	2.49	(2.46, 2.51)	2.26	(2.23, 2.28)

B: Betel quid chewing only; BS: Betel quid chewing and cigarette smoking; CI: incredible interval; S: cigarette smoking only; * PM$_{2.5}$ with dichotomous were estimated in different model, adjusted by sex, age, and oral habit (betel quid chewing and cigarette smoking).

and cigarette smoking, the significant effect of PM$_{2.5}$ on OPMD/OC still remains with an increased adjusted risk of 11% (adjusted RR (aRR) = 1.11, 95% CI: 1.09⁻1.13). When categorized PM$_{2.5}$ by 10 µg m^{-3}, the risks of OPMD/OC were significantly higher in the groups in the univariable and the multivariable analyses. The aRRs of OPMD/OC were 1.20 (95% CI: 1.16–1.24), 1.36 (95% CI: 1.31–1.40), 1.39 (95% CI: 1.34–1.44), and 1.52 (95% CI: 1.46–1.57) in the PM$_{2.5}$ concentration groups of 10–19, 20–29, 30–39, ≥ 40 µg m^{-3}, respectively, after adjusting for age, sex, betel quid chewing and cigarettes smoking (Table 2).

Dose-response relationships of oral habits and OPMD or OC has been demonstrated in previous studies and we chose some typical papers with comparable attributes of oral habits in Taiwan or India (Madathil *et al.*, 2016; Yang *et al.*, 2010; Yen *et al.*, 2007; Znaor *et al.*, 2003). As shown in previous studies, the higher the quantity of cigarette smoking or betel quid chewing, the higher the risk of OPMD/OC. As shown in Fig. 3(a), the concentration-dependent effect of PM$_{2.5}$ can be observed in comparison with magnitude of effects of traditional risk factors (betel quid and cigarette smoking).

Many studies have reported that exposure to PM$_{2.5}$ increased the risk of lung cancer or respiratory diseases (Ghazipura *et al.*, 2019; Hamra *et al.*, 2014; Hopke *et al.*, 2019; Raaschou-Nielsen *et al.*, 2016). Undoubtedly, oral is one of the exposure routes to these ultrafine particles. Biological evidence has been established for plausible mechanisms between PM$_{2.5}$ and carcinogenesis, such as increased oxidative stress, induced DNA damages and DNA mutations, inflammatory responses, and may lead to the occurrence of malignant tumor (Feng *et al.*, 2016; Ghio *et al.*, 2012). Furthermore, OC/OPMD is mostly developed from the squamous cell, in that accounted to 80–90% of oral malignancy (Johnson *et al.*, 2011). Thus, inflammatory response maybe be one of the mechanisms underpinning the association between PM$_{2.5}$ and OPMD/OC.

3.2 PM$_{2.5}$ and Risk of OPMD

The highest average PM$_{2.5}$ concentration was noted in Chiayi City with the mean of 34.00 µg m^{-3} (SD: 14.50 µg m^{-3}) and the lowest average concentration was found in Taitung County with the mean of 11.81 µg m^{-3} (SD: 3.88 µg m^{-3}) (Table S3). The proportion of diagnosed OPMD cases by county/city was shown in Fig. 2(b). The highest proportion of diagnosed cases was found in Chiayi City (7.83%), followed by Penghu County (6.48%) and Changhua County (6.26%) and the lowest proportion was found in Hsinchu County (1.23%), see Table S4.

The effect of PM$_{2.5}$ and others related factors on OPMD are elucidated in Table 3. In the
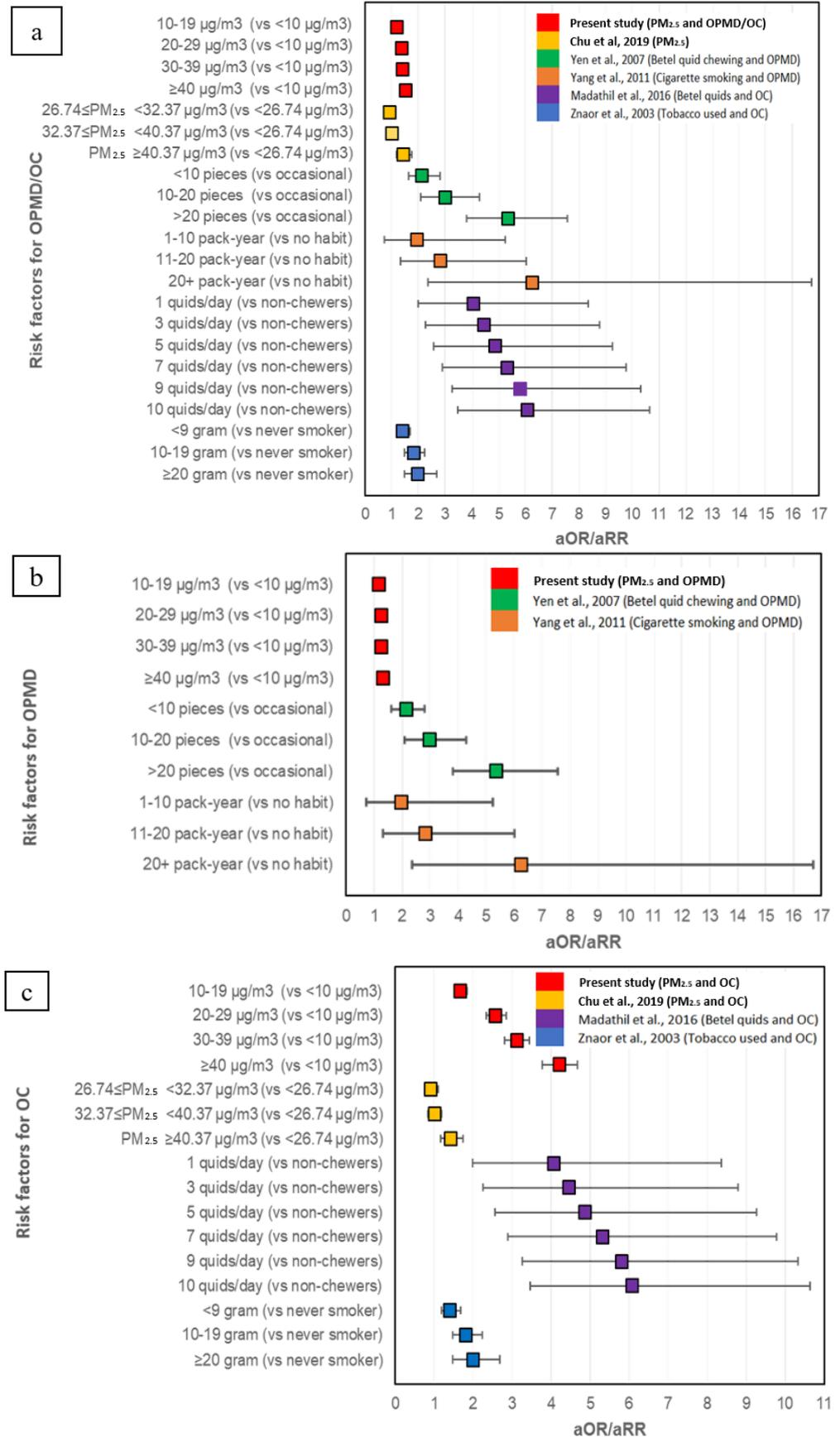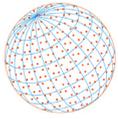
Fig. 3. Adjusted odds/relative risk ratio of PM$_{2.5}$ and other risk factors for (a) OPMD or oral cancer (b) OPMD and (c) OC.
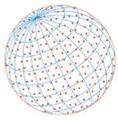
Table 3. Univariable and multivariable Bayesian random-effect logistic regression models for OPMD.

Variables	RR	(95% CI)	aRR	(95% CI)
$PM_{2.5}$ (vs < 35 µg m^{-3})*				
≥ 35 µg m^{-3}	0.98	(0.97, 1.00)	1.04	(1.03, 1.06)
$PM_{2.5}$ (vs < 10 µg m^{-3})				
10–19 µg m^{-3}	1.05	(1.02, 1.09)	1.15	(1.11, 1.19)
20–29 µg m^{-3}	1.08	(1.04, 1.11)	1.26	(1.21, 1.30)
30–39 µg m^{-3}	1.04	(1.01, 1.08)	1.25	(1.20, 1.29)
≥ 40 µg m^{-3}	1.06	(1.03, 1.10)	1.30	(1.25, 1.35)
Sex (vs Female)				
Male	5.32	(5.20, 5.43)	4.57	(1.50, 1.54)
Age group (vs 70+, years)				
30–49	2.15	(2.11, 2.20)	2.23	(2.18, 2.28)
50–69	2.32	(2.28, 2.37)	2.40	(2.34, 2.45)
Habit (vs S)				
B	0.83	(0.81, 0.85)	1.15	(1.12, 1.18)
B + S	2.42	(2.39, 2.45)	2.23	(2.20, 2.26)

B: Betel quid chewing only; BS: Betel quid chewing and cigarette smoking; CI: incredible interval; S: cigarette smoking only; * $PM_{2.5}$ with dichotomous were estimated in different model, adjusted by sex, age, and oral habit (betel quid chewing and cigarette smoking).

univariable analysis, $PM_{2.5}$ exposure was insignificant associated with OPMD. However, higher $PM_{2.5}$ significantly increased the risk of OPMD by 4% (aRR = 1.04, 95% CI: 1.03–1.06) in the multivariable analysis. When categorized $PM_{2.5}$ by 10 µg m^{-3}, the risks of OPMD/OC were significantly higher in the $PM_{2.5} > 10$ µg m^{-3} concentration groups in the univariable and the multivariable analyses. These concentration-dependent relationships can be observed, and compared to the magnitude of effects of traditional risk factors (betel quid and cigarette smoking) as shown in Fig. 3(b).

Recent study has shown one of the cardiovascular related-inflammatory markers, the CRP was increased with high level of $PM_{2.5}$ in adults with MetS (Dabass *et al.*, 2018). MetS has been found to be associated with OPMD and several cancers (Braun *et al.*, 2011; Ku *et al.*, 2019; Siewchaisakul *et al.*, 2020; Yen *et al.*, 2011). Pro-inflammatory markers, including TNF-α, IL-6 and CRP were shown to be the underlying mechanism between MetS and OPMD as well (Hsu *et al.*, 2014).

3.3 $PM_{2.5}$ and Risk of OC

The highest average $PM_{2.5}$ concentration was noted in Chiayi City with the mean of 33.98 µg m^{-3} (SD: 14.48 µg m^{-3}) and the lowest average concentration was found in Taitung County with the mean of 11.83 µg m^{-3} (SD: 3.88 µg m^{-3}) (Table S5). The proportion of diagnosed OC cases by county/city was shown in Fig. 2(c). The highest proportion of diagnosed cases was found in Chiayi City (1.23%), followed by Changhua County (1.23%) and Yunlin County (1.00%) and the lowest proportion was found in Lianjiang County with no case found in our study, see Table S6.

The effect of $PM_{2.5}$ and others related factors on OC are elucidated in Table 4. In the univariable analysis, $PM_{2.5}$ with concentration greater than or equal to 35 µg m^{-3} shown significantly increased risk of OC by 44% (RR = 1.44, 95% CI: 1.39–1.50) compared to those lower than 35 µg m^{-3}. In the multivariable analysis, higher $PM_{2.5}$ exposure statistically increased the risk of OC by 55% (aRR = 1.55, 95% CI: 1.49–1.60) compared to low $PM_{2.5}$ exposure. When categorized $PM_{2.5}$ by 10 µg m^{-3} in the multivariable analysis, $PM_{2.5}$ still increased risk of OC with higher concentrations. $PM_{2.5}$ with concentration of 10-19 µg m^{-3} has greater risk of OC by 1.68-fold compared to those lower than 10 µg m^{-3} (aRR = 1.68, 95% CI: 1.52–1.85). This result is consistent with the concentrations of 20–29, 30–39, ≥ 40 µg m^{-3} compared to < 10 µg m^{-3} in which the aRR were 2.58 (95% CI: 2.33–2.85), 3.12 (95% CI: 2.81–3.45), and 4.21 (95% CI: 3.78–4.68), respectively (Table 4).

These concentration-dependent relationships were commensurate with the magnitude of effects of traditional risk factors (betel quid and cigarette smoking) as shown in Fig. 3(c). The
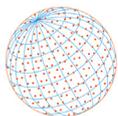
Table 4. Univariable and multivariable Bayesian random-effect logistic regression models for OC.

| Variables	RR	(95% CI)	aRR	(95% CI)
PM$_{2.5}$ (vs < 35 µg m^{-3})*				
$\geq$ 35 µg m^{-3}	1.44	(1.39, 1.50)	1.55	(1.49, 1.60)
PM$_{2.5}$ (vs < 10 µg m^{-3})				
10–19 µg m^{-3}	1.57	(1.42, 1.73)	1.68	(1.52, 1.85)
20–29 µg m^{-3}	2.27	(2.04, 2.51)	2.58	(2.33, 2.85)
30–39 µg m^{-3}	2.65	(2.38, 2.93)	3.12	(2.81, 3.45)
$\geq$ 40 µg m^{-3}	3.44	(3.09, 3.79)	4.21	(3.78, 4.68)
Sex (vs Female)				
Male	7.99	(7.50, 8.50)	7.42	(6.95, 7.94)
Age group (vs 70+, years)				
30–49	0.86	(0.83, 0.90)	1.00	(0.96, 1.04)
50–69	1.69	(1.62, 1.75)	1.90	(1.82, 1.98)
Habit (vs S)				
B	1.45	(1.38, 1.54)	1.82	(1.72, 1.93)
B + S	3.02	(2.93, 3.12)	2.48	(2.40, 2.56)

B: Betel quid chewing only; BS: Betel quid chewing and cigarette smoking; CI: incredible interval; S: cigarette smoking only; * PM$_{2.5}$ with dichotomous were estimated in different model, adjusted by sex, age, and oral habit (betel quid chewing and cigarette smoking).

higher the quantity of cigarette smoking or betel quid chewing, the higher the risk of OC. The same trend could also be found for the association between PM$_{2.5}$ exposure and risk of OC, consistent with previous study reported by Chu *et al.* (2019).

The components of PM$_{2.5}$, such as arsenic, nickel, chromium, asbestos, and polycyclic aromatic hydrocarbons (PAHs), have been found to be associated with an increased OC risk (Gutiérrez-Castillo *et al.*, 2006; Paget-Bailly *et al.*, 2012; Su *et al.*, 2010; Yuan *et al.*, 2011). The carcinogenetic potential of chronic PM$_{2.5}$ exposure has been widely demonstrated in animal studies, with genome wide epigenetic and RNA transcription changes and malignant cancer cell behaviors such as cross-talk between epithelial-mesenchymal transition (EMT) and cancer stem cells (CSCs) properties which may lead to enhanced tumorigenicity and promote cancer cell progression (Yang and Xiao, 2018; Lee *et al.*, 2020). These together may explain the association of PM$_{2.5}$ and OPMD/OC, as well the reason why the association between PM$_{2.5}$ and OC is more profound than OPMD in this study.

3.4 Comparison between Studies

To our knowledge, only limited epidemiological studies have reported PM$_{2.5}$ and OC risk. A previous study in Taiwan has reported that an increased risk of OC among men who were exposed to PM$_{2.5}$ concentration over 40.37 µg m^{-3} (aOR = 1.43, 95% CI: 1.17–1.74), compared with 26.74 µg m^{-3} < PM$_{2.5}$ (Chu *et al.*, 2019). We targeted smokers and/or betel quid chewers, the high-risk population of OPMD/OC and found that PM$_{2.5}$ with concentration of 35 µg m^{-3} and higher has a significant increased risk of OC, and the effect magnitude in associated with OC was even higher compared to others. We also found that PM$_{2.5}$ with concentration of 10 µg m^{-3} and higher has a significant increased risk of OPMD. The novelties of this study could be emphasized by comparing to the previous studies. First, our study is a longitudinal cohort study with 11 years followed-up of OPMD/OC nationwide screening data. This makes allowance for the identification of OPMD cases, the precursor of invasive oral cancer, as well as the information on both sexes and unhealthy oral habits. Second, we took into account the geographic variations when evaluating the OC risk in association with PM$_{2.5}$ in our study. We consider monthly average PM$_{2.5}$ concentration as a random effect in our model since this exposure indicator is a hierarchical factor rather than an individual one. Last but not least, an ecological study by Su *et al.* (2019) presented the geographical variations on the association between PM$_{2.5}$ and cancer incidence in Taiwan. Su *et al.* (2019) also reported a significant dose-response relationship between PM$_{2.5}$ and OC incidence with spearman correlation ranged between 0.56–0.59 in men. However, several potential risk factors such as habitual smoking or betel quid chewing were not considered in their study.
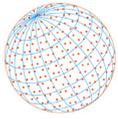
3.5 Limitation

Some limitations in this study should be noted. First, we do not have exact data on individuals' daily $PM_{2.5}$ exposures. Therefore, we estimated monthly $PM_{2.5}$ concentration in average by areas. Second, we used data based on nationwide OC screening program in which targeted population were those who only experienced betel quid chewing or smoking behavior. Thus, generalization of our study results would limit to smokers and/or betel quid chewers. Third, the $PM_{2.5}$ exposure duration and the exposure history has not been considered in this study. Those who were diagnosed as oral cancer might have been continuously exposed to high level of $PM_{2.5}$. Finally, there are still numerous variables related to OPMD/OC risk such as genetic, family history of OC, history of chronic diseases and other potential carcinogenic compounds, which we haven't considered in this study.

4 CONCLUSIONS

To our knowledge, this is the first study to investigate the association between $PM_{2.5}$ and OPMD/OC at nationwide level. Based on the longitudinal nationwide OC data, we found that $PM_{2.5}$ exposure was linked to an increased risk of OPMD/OC among smokers and/or betel quid chewers. Our results also demonstrated the spatial variations for $PM_{2.5}$ concentration and OPMD/OC. This information would beneficial to OPMD/OC prevention policy in some specific counties or cities. Future studies are warranted to investigate the effect of personal $PM_{2.5}$ exposure on OPMD/OC risk.

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SUPPLEMENTARY MATERIAL

Supplementary material for this article can be found in the online version at https://doi.org/10.4209/aaqr.210060

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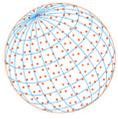
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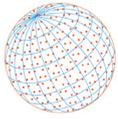
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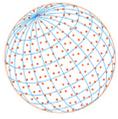
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