Flavor Disorder Is Associated with Obstructive Sleep Apnea: A Nationwide Population-Based Cohort Study

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Research Article

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Abstract

Background: Flavor sensation was the joint perception of smell and taste sensation was associated with the pleasure of life. Obstructive sleep apnea (OSA) had been demonstrated the presence of upper airway remodeling which altered sensory and motor function due to hypoxia or snore vibration. This study aims to investigate whether OSA is associated with the risk of flavor disorder (FD).

Methods: We conducted a nationwide cohort study using the Taiwan National Health Insurance Research Database, one million subjects were sampled with data collected from 1999 to 2013 and 9,191 identified diagnosed OSA patients were included. Each patient was matched with non-OSA controls from the general population by propensity score matching (1:1) based on age, gender, hypertension, hyperlipidemia, ankylosing spondylitis, and Charlson comorbidity index, 8,037 OSA and an equal number of non-OSA subjects were used to compared in this study. The incidence of FD was assessed at the end of 2013 and cumulative incidences, hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated.

Results: The adjusted HR (aHR)of FD for the OSA group was 2.082-fold (95% CI = 1.149–3.773, p=0.0155) higher than non-OSA group. The stratified analyses revealed aHR of FD for the hyperlipidemia group was 2.264-fold (95% CI = 1.061–4.832, p=0.035). Subgroup analysis showed the subjected of female OSA had more risk to develop FD (aHR:2.345, 95% CI = 1.026–5.357, p=0.043).

Conclusion: A higher risk of developing FD was found among the newly diagnosed OSA cohort during the longer than 10-year follow-up period

Statement Of Significance

The study cohorts were large enough to observe the risk variations among subgroups and delved into a possible association about patients with newly diagnosed obstructive sleep apnea (OSA) and higher risk of flavor disorder (FD), we demonstrated a 2.082-fold greater risk of subsequent development of FD among OSA patients than the general population, and 2.264-fold greater risk to develop FD amount group with hyperlipidemia.Furthermore, the stratified analyses revealed significant effects of female OSA patient with exposure 2.345-fold greater risk than OSA male, OSA patients without hypertension were developing 2.440-fold risk to develop FD than non-OSA patients without hypertension. Instead, there was no significant difference in FD between the sub group of hyperlipidemias with OSA and non-OSA, it is speculated that the side effects of anti-hyperlipidemia agent are greater than the impact of OSA on flavor sensation.

Introduction

Compared to visual, auditory, painful sensation or motor defects, loss of taste, somatosensory, and olfactory damage are generally regarded less to cause immediate attention. However, taste and olfactory disorder diminish the pleasures of life. Flavor sensation (FD) is defined as a unitary perception derived from multiple sensory afferents, including the joint perception of taste, smell and somatosensory [1].

Taste sensation provides important sensory cues for regulating complex autonomic nerve activities. Such as sour taste has been shown to be associated with parotid salivary flow for initiating digestion[2], Salty taste stimulates the pancreatic and hepatic branches of vagus nerve[3], Sweet taste increases gastric acid secretion by exciting the vagus nerve[4], umami sensation elicited by L-glutamate(glu) stimulates palatability and induces pleasure in gustation[5]. In terms of nutrient homeostasis and modulation of digestion, taste sensation plays multiple important roles.
The general role of smell sensory is guiding our attention to avoiding hazards (e.g., smoke and microbial threats) and mainly in food intake, the discrepancies between expectation and perceived flavor can lead to appetite regulation. [6, 7]. Smell sensory also be involved in social communication, via the odors, the mate selection and reproductive behavior can be proceeded. [8] Smell disorder directly reduce food enjoyment, affected in social security and professions depending on olfactory ability (e.g., medical staff, sommelier, cooks, perfumers) may lead to disturbance in important areas and make persons more prone to depression [9]. However, unawareness of olfactory loss was common in general population and prevalence of smell and taste impairment were seem be estimated lower than true prevalence rates [10,11].

Recent study had shown that patients with OSA were under the risk of hyposmia even anosmia due to hypoxia and lower nasal flow [12]. Some report had discussed the association about neuropathies on olfactory, cold sensory over the upper airway [13-14]. As a chronic disease syndrome, OSA had been characterized by recurrent nasal, oropharyngeal or hypopharyngeal obstruction and vigorous snoring[15-16], which provokes local inflammation as leukocyte accumulated in oral mucosa or peripheral nerve injury due to snore related vibration[17-18], cause hypoxia, hypoventilation and hypoxemia in system[19], impaired vascular endothelial function and peripheral perfusion[20],affects integrity of vascular endothelium and coagulation thus linked to autoimmune disease[21-23 ], in addition, emotion, judgment, and cognition in mental were involvement in human[24-26].

In 1993, the prevalence of OSA were reported about 2~4% in North America by the definition of apnea–hypopnea index, AHI ≥5 [27]. As the time going, even with the more stringent definition of AHI ≥15 events per hour, the estimated prevalence is increased to around 15 % in males and 5 % in females with the same Wisconsin sleep cohort in 2013 [28]. A recent population-based study demonstrated a need to revise the definition of this disease in Switzerland, and proposed a high prevalence of moderate to severe OSA (AHI≥15) (23.4% for women, 49.7% for men) [29]. In addition to increasing numbers of consultations, sleep-related surgery was become popular and all above factors may affect the sense of taste, smell and somatosensory [1,30]. Flavor is a perception of anatomically separated functionally united, a complete sense of flavor is based on a complete taste and smell, even somatosensory and memory. Overall, taste and oral somatosensory cues combine centrally with retro nasal olfactory to produce the composite experience of flavor sensation.

Therefore, this longitudinal nationwide cohort study was conducted to explore the risk of FD between OSA and general people, whether patients with newly diagnosed of OSA was prone to develop (FD) than general population subsequently, which was not been discussed in a large-scale population-base cohort of single race.

Material And Methods

Data source

The data source for this cohort study was reimbursement claims data from Taiwan's National Health Insurance (NHI) program. The reliability of the NHIRD diagnostic codes has been supported by a recent validation study [31]. Mandatory insurance policies mean that more than 99% of the 23 million people of Taiwan participate in the universal health insurance program [32]. One million subjects were sampled from the population and collected the data from 1999 to 2013. The incidence of FD was assessed at the end of 2012.

Patient and Public involvement

From 2000 to 2012, we identified 9,191 newly diagnosed OSA, excluded 1,149 subjects with
diagnosis of disturbances of sensation of smell and taste or cancer before index date and 5 patients death before censor date, finally match with 8,037 non-OSA subjects included in this study after propensity score matching (1:1) based on age, gender, hypertension, hyperlipidemia, ankylosing spondylitis and Charlson comorbidity index. There was long follow-up time with high similarity between both groups after propensity matching. The study was approved by the institutional review board of Chung Shan Medical University (IRB number: CS15134). All methods were carried out in accordance with relevant guidelines and regulations.

_**Patients with obstructive sleep apnea (OSA)**_

From 1999 to 2012, newly diagnosed OSA (ICD-9-CM codes 327.23, 780.51, 780.52, 780.53 and 780.57) by otolaryngologist or pulmonologist were included in the OSA group. Only patients with $\geq 3$ outpatient visits or at least 1 inpatient admission on or after 1 January 2000 were included in the OSA cohort. The date of $\geq 3$ outpatient visits (including the index visit) or at least 1 inpatient admission on or after 1 January 2000 due to OSA was defined as the index date. The index date anchored the start of follow-up (supplement Figure1). Patient with first diagnosis of flavor disorder before index date were excluded from the OSA cohort. The non-OSA group was never diagnosed of obstructive sleep apnea from 1999 to 2013.

_**Propensity Scores**_

Generalized propensity scores based on the probability of being in both groups were used to decreased the potential confounders, firstly, a 1:4 age and gender matching was used to give the index date corresponding to the non-OSA cohort. The propensity score matching (1:1) was used to establish non-OSA cohort based on age, gender and preexisting comorbidities including hypertension, hyperlipidemia, ankylosing spondylitis, and Charlson comorbidity index.

_**Identified patients of flavor disorder (FD)**_

The date of first diagnosis of flavor disorder (FD) (ICD-9CM codes 781.1) during the follow-up period was defined as the primary endpoint. ICD-9 CM codes used in this study included those for flavor disturbance including disturbances in sensation of smell or taste. All patients were tracked from the index date to the date of diagnosis of flavor disorder, withdraws from the Mandatory insurance or death before censor date during the period of follow up have been eliminated before the screening for inclusion. The matched samples are also eligible for those who did not withdraw or death within the tracking period.

_**Statistical analysis**_

Demographic data, between qualified OSA and non-OSA groups were analyzed with Chi-square test or independent T test. Kaplan-Meier method was used to describe the cumulative incidences of flavor disorder among the two groups with differences between the groups evaluated by log rank test. Cox's proportion hazard model was conducted to measure the effects of OSA on the risk of flavor disorder.

Data was processed and analyzed using SPSS software Version 18.0 (SPSS Inc., Chicago, IL, USA). The significance level was set at 2-tailed $p$ value of 0.05.

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**Results**

After applying the inclusion and exclusion criteria and carrying out age-sex matching, 8,037 OSA and equal number of non-OSA subjects were enrolled (Figure 1), table 1 indicates that most of the patients included in the study were age 40-65 (OSA group, n=4044, 50.3%), 44.4% were female, 24.1% were with hypertension, 11.7% were with hyperlipidemia and 0.3% were with ankylosing spondylitis, among whom 35.7% of the patient’s Charlson comorbidity index (CCI) \( \geq 1 \). Totally, 14.5% (1,162/8,037) OSA patient accept surgery, including tonsillectomy, adenoid tonsillectomy and UPPP (surgical code: 71006, 71008, 66025). Table 1 compared the demographic characteristics of OSA cohort and non-OSA cohort after propensity score matched.

Figure 2 indicated the cumulative proportions of FD in both groups, according to the test for proportional assumption and slope of Kaplan-Meier curves, there were higher cumulative proportion of FD in OSA groups and were with significant statistically difference \( (p = 0.013) \). After adjusting for age, gender, preexisting comorbidities, including hypertension, hyperlipidemia and ankylosing spondylitis, and Charlson comorbidity index. The risk of FD in OSA is time dependent.

Table 2 presents crude HRs and adjusted HRs (aHR) of flavor disorder for subgroups of OSA, non-OSA, age stratified, gender, hypertension, hyperlipidemia, and stratified of CCI after propensity score matched. On univariate modeling, the crude HR of OSA group was 2.081 (95% C.I. = 1.149-3.770, \( p = 0.0156 \)), the aHR was 2.082 (95% C.I. = 1.149-3.773, \( p < 0.0155 \)). When age was stratified as <20, 20-40, 40-65 and \( \geq 65 \), the aHR of FD in 40-65 group (2.042, 95% C.I. = 0.951-4.386, \( p = 0.067 \)) was higher than the other subgroup of age but significance was not reached for any stratified age group. When stratified by gender, female group had higher adjusted HR than male group (1.448, 95% C.I. = 0.827-2.543, \( p = 0.195 \)), but the difference was not significant. So do the result of Hypertension (0.871, 95% C.I. = 0.423-1.794, \( p = 0.708 \)). In the comorbidity of hyperlipidemia, the crude HR was 2.271 (C.I. = 1.134-4.550, \( p = 0.021 \)) and the aHR was 2.264 (C.I. = 1.061-4.832, \( p = 0.035 \)) in FD. Trace to deadline, no event of FD in subgroups of ankylosing spondylitis (AS) and Charlson comorbidity index (CCI \( \geq 1 \)), so we remove the AS from Cox model analysis and dichotomy (0/\( \geq 1 \)) was used to analyze by the Cox model. The incidence rates (pre 1000 person years) of FD were higher in OSA cohort than in non-OSA cohort (0.70 and 0.34/1000 person-years), in females (0.64 and 0.43/1000 person-years) and in 40-65 age group (compared to <20 age, 0.69 vs 0.43). Among the preexisting comorbidity subgroups, OSA and hyperlipidemia showed significantly higher aHR.

Table 3 shows the results of subgroup analysis. The female OSA patient exposure increased risk to develop FD (aHR was 2.345, 95% C.I. = 1.026-5.357, \( p = 0.043 \)) for female of non-OSA, on stratified analysis of non-hypertension, there were 2.440-fold of aHR (95% C.I. = 1.210-4.919, \( p = 0.013 \)) to develop FD on OSA group with non-hypertension than non-OSA group with non-hypertension. On hyperlipidemia stratified analysis \( (p \text{ for interaction } = 0.083) \), OSA with hyperlipidemia were with 3.952 aHR of develop FD (95% C.I. = 0.838-18.648) than non-OSA with hyperlipidemia, but no statistically significant \( (p = 0.083) \). Among the preexisting OSA subgroups, female and non-hypertension showed significantly higher aHR to develop FD.

**Discussion**

This is the first study to determine that patients with OSA exhibited a 2.082-fold greater risk of subsequently developing flavor disorder than did the general population after propensity score matching by using a nationwide
population-based cohort study. Furthermore, the effects of OSA were found to be significant in subgroups of non-hypertension patients.

This population-based follow-up study possesses several unique characteristics. First, our OSA subjects were newly diagnosed by otolaryngologist or pulmonologist and fit the criteria of ≥3 outpatient visits (including the index visit) or at least 1 inpatient admission. This is a more rigorous method of sample collection than following examination codes of polysomnography (PSG, examination codes: 17008A and 17008B in HNIRD) as OSA patients accept therapy from otolaryngologist or pulmonologist, while many non-OSA patients accept PSG also. Second, the selection of our control group was based on propensity score matching. Therefore, comorbidities were controlled. Third, 99% of the population in Taiwan is insured and almost all patients are comprehensively followed up with medical and even surgical services.

There are several possible reasons for the increase in risk of FD in OSA. First, the common theory is that inherent vibration injury to soft tissue over oropharynx leads to peripheral neuropathy or hypoxia both [17-19]. Second, surgery induces flavor disorder [33]. Due to high availability and low cost, one population-based study using NHIRD from 2002-2010 showed that 17.9% (922/5139) of patients accept surgery for OSA including oropharyngeal surgery and nasal surgery [32]. Our data showed 14.5% OSA patient accept surgery over oropharynx, including tonsillectomy, adenoid tonsillectomy and UPPP (surgical code:71006,71008,66025) which may impact to gustatory. Subjected with persistent taste disorders and smell disorders after surgery would be recorded in the diagnostic code. Previous research demonstrated that the percentage of temporal subjective gustatory changed after tonsillectomy is nearly 60/188 (32%) at 2 weeks and 15/181 (8%) at more than 6 months [34]. There may have some effect to our result. Therefore, we roughly estimate that will increase the 4.64~1.16% (14.5% times 32% or 14.5% times 8%) risk of FD in OSA group.

There is some evidence to suggest that there are no fundamental taste differences associated with hypertension and patients with hypertension have higher recognition threshold for salt [35]. An animal study has shown an association between hypertension and salt preference when Ang-II type II angiotension receptors in rat brain are stimulated [36-37]. Moreover, some studies have illustrated that hypertensive humans have a preference for salty as salt-sensitive rats [38-39]. Although some species of antihypertensive drugs may alter taste (e.g., ACEI inhibitors, some calcium-channel blockers), some agents can produce a prolonged bitter taste (e.g., β-adrenergic receptor blockers, rilmenidine and antiarrhythmic agents) [40], diuretics and α/β adrenergic blockers were less impact to altered taste or induce ageusia [41]. Therefore, from the characteristics of hypertension itself and the enhancement or reduction of anti-hypertensive agents to chemoreceptor, hypertension is not a risk factor for flavor disorder. Our data showed that aHR (0.871) is lower than in control groups in hypertension, indeed is lower, but not significant(\( p=0.708 \)).

Many studies have demonstrated associations for hyperlipidemia and antihyperlipidemic drug use with development of FD. One large cross-sectional study showed that flavor dysfunction is related to higher concentration of LDL-C (P-trend =0.07), the development of dyslipidemia may be a harbinger of future diabetes and may influence chemoreceptors[42]. A limited number of studies have illustrated that 70% of patients have altered taste after taking hydroxymethylglutaryl-coenzyme A(HMG-CoA) reductase inhibitors(e.g. atorvastatin calcium, fluvastatin sodium, simvastatin, lovastatin and pravastatin sodium)[41].

The group of hyperlipidemias had taken HMG-CoA commonly in Taiwan, table 2 showed 2.264-fold of FD for risk of hyperlipidemias to non-hyperlipidemia(\( p=0.035 \)), which were contained the patient with hyperlipidemia who had taken or had not taken HMG-CoA. However, the subgroup analysis of table 3 showed there were no difference for FD development between hyperlipidemia with OSA and hyperlipemia without OSA (\( p \) for interaction was 0.083). If there
persist a hypothesis that the side effect of anti-hyperlipidemia agents were more stronger than OSA to develop FD? It's may due to the interference of drug side effects, high availability and low cost of medical environment. This result can be left to subsequent data confirm.

Gender difference in taste sensitivity has been reported, with females being more sensitive to flavor change. Many researchers have demonstrated that women have greater taste perception than men based on different taste scores[43-46]. Table 2 showed no risk of gender difference in general condition (aHR:1.448, p=0.195) but subgroup analysis illustrated woman with OSA had 2.345-fold aHR (p<0.05), whether women's flavor sensation was more sensitive to external factors such as hypoxia of OSA, vibration trauma of oropharyngeal mucosa from snoring may need further research to confirm.

Several limitations of this study should be considered when interpreting the results. First, although we obtained a large population with OSA, surgery and medical-seeking behavior were confounding factors due to accessible and convenient medical consumption. For example; 1162 (14.5%) OSA patient accept surgery , estimated literature on the incidence of FD after surgery, that will increase the 4.64~1.16% risk of FD in OSA group, of the same reason to the group of hyperlipidemias had taken HMG-CoA commonly, Therefore, there may be selection bias and this study cohort may not be entirely representative of the population in other country. Second, the severity of OSA is unavailable in the NHIRD, including treatment statuses and improvements in flavor sensation. Third, our study utilized a nationwide administrative claims database and the diagnoses of medical comorbidities were solely based on ICD-9-CM codes from the NHIRD. The validity of diagnosis needs to be checked where misclassification might exist. Although there are no unified criteria for the diagnosis of OSA, most sleep centers in Taiwan strictly follow the guidelines of AASM (American Academy of Sleep Medicine) for the diagnosis of OSA, meaning the combination of clinical symptoms and PSG test.

However, arranging polysomnography exam were not expensive or even too popular under Taiwan's health insurance system. People of non-OSA (AHI<5) people may be mis-arranged to OSA group. Due to the result about polysomnography were unavailable in the NHIRD database, it may not be the most appropriate way to use polysomnography as a diagnosis of OSA. There for, we introduce a more rigorous method(≧3 outpatient visits or at least 1 inpatient admission) to increase robustness of diagnostic accuracy of OSA cohort. The same methodology was used in some population base research as below for more rigorous diagnosis as ankylosing spondylitis[47].

**Conclusion**

This 12-13-year population-base cohort study demonstrated a higher risk of developing FD in patient with OSA and women with OSA may be more sensitive. Clinicians need to provide appropriate monitoring for the high-risk patients.

**Declarations**

**Conflict of interest:** The authors declare that there is no conflict of interests regarding the publication of this paper.

**Contributors:** This study was supported by Chung Shan Medical University DryLab Team and granted by Chung Shan Medical University Hospital; James Cheng-Chung We is leader. Hsin-Hsin Huang, Chien Han Tsao , Yin-Tsan Hung, James Cheng-Chung Wei and Yao-Min Hung conceived and designed the study. James Cheng-Chung Wei provided administrative support. Chien Han Tsao , Yao-Min Hung and Yu-Hsun Wang analyzed and interpreted the data. Hsin-Hsin Huang, Chien Han Tsao , Yao-Min Hung, Wei-Sheng Wen contributed by writing the manuscript. All authors were involved in collection and assembly of data. Hsin-Hsin Huang and Yao-Min Hung contributed equally to this work.
Chien Han Tsao was corresponding authors, James Cheng-Chung Wei contributed and Yin-Tsan Hung equally to this work. All authors approved the final version of the manuscript to be published.

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**Tables**

Table 1. Characteristics and comorbidities amount sleep apnea syndrome cohort and non-sleep apnea syndrome cohort after propensity score matched
|                      | Sleep apnea syndrome (N =8037) | Non-Sleep apnea syndrome (N =8037) | p-value |
|----------------------|---------------------------------|-----------------------------------|---------|
|                      | n   | %   | n   | %   |         |
| Age                  |     |     |     |     | 0.999   |
| <20                  | 316 | 3.9 | 317 | 3.9 |         |
| 20-40                | 2321| 28.9| 2313| 28.8|         |
| 40-65                | 4044| 50.3| 4045| 50.3|         |
| ≥65                  | 1356| 16.9| 1362| 16.9|         |
| Mean ± SD            | 48.0±16.9 |     | 48.8±17.0 |     |         |
| Gender               |     |     |     |     | 0.975   |
| Male                 | 4469| 55.6| 4471| 55.6|         |
| Female               | 3568| 44.4| 3566| 44.4|         |
| Hypertension         | 1934| 24.1| 1935| 24.1| 0.985   |
| Hyperlipidemia       | 944 | 11.7| 940 | 11.7| 0.922   |
| Ankylosing Spondylitis| 22  | 0.3 | 11  | 0.1 | 0.055   |
| CCI†                 |     |     |     |     | 0.818   |
| 0                    | 5169| 64.3| 5155| 64.1|         |
| ≥1                   | 2868| 35.7| 2882| 35.9|         |
| Surgery*             | 1162| 14.5|     |     |         |

†Charlson comorbidity index; *p<0.05, **p<0.01.

*Surgery : tonsillectomy, adenotonsillectomy, uvulopalatopharyngoplasty

Table 2. Estimation the hazard ratios of flavor disorder by using Cox proportional hazard model
| No. of flavor disorder | Observed Person-Years | Incidence Density (Per 1000 Person-Years) | Crude HR | 95% C.I. | p-value | Adjusted HR† | 95% C.I. | p-value |
|-----------------------|-----------------------|------------------------------------------|----------|---------|--------|--------------|---------|--------|
| **Exposure of OSA**   |                       |                                          |          |         |        |              |         |        |
| (ref: non OSA)        |                       |                                          |          |         |        |              |         |        |
| Non-OSA               | 16                    | 47303                                    | 0.34     | 1       |        |              |         |        |
| OSA                   | 34                    | 48307                                    | 0.70     | 2.081   | 0.0156 | 2.082       | 0.149-3.773 | 0.0155 |
| **Age**               |                       |                                          |          |         |        |              |         |        |
| <20                   | 2                     | 4621                                     | 0.43     | 1.384   | 0.678  | 1.444       | 0.311-6.698 | 0.639 |
| 20-40                 | 9                     | 28885                                    | 0.31     | 1       | 1      |              |         |        |
| 40-65                 | 33                    | 47784                                    | 0.69     | 2.226   | 0.033  | 2.042       | 0.951-4.386 | 0.067 |
| ≥65                   | 6                     | 14320                                    | 0.42     | 1.356   | 0.564  | 1.265       | 0.417-3.839 | 0.678 |
| **Gender**            |                       |                                          |          |         |        |              |         |        |
| Male                  | 23                    | 53219                                    | 0.43     | 1       |        |              |         |        |
| Female                | 27                    | 42391                                    | 0.64     | 1.468   | 0.176  | 1.448       | 0.827-2.534 | 0.195 |
| Hypertension          | 12                    | 20875                                    | 0.57     | 1.140   | 0.693  | 0.871       | 0.423-1.794 | 0.708 |
| Hyperlipidemia        | 10                    | 9579                                     | 1.04     | 2.271   | 0.021  | 2.264       | 1.061-4.832 | 0.035 |
| **CCI†**              |                       |                                          |          |         |        |              |         |        |
| 0                     | 32                    | 62499                                    | 0.51     | 1       |        |              |         |        |
| ≥1                    | 18                    | 33111                                    | 0.54     | 1.063   | 0.836  | 0.887       | 0.476-1.654 | 0.706 |

†Adjusted for age, gender, hypertension, hyperlipidemia, and Charlson comorbidity index.

Table 3. Subgroup analysis between Sleep apnea syndrome cohort and Non-Sleep apnea syndrome cohort by using Cox proportional hazard regression
|                | Sleep apnea syndrome | Non-Sleep apnea syndrome | aHR‡ | 95% C.I.     | p-value |
|----------------|----------------------|--------------------------|------|--------------|---------|
| **Age**        |                      |                          |      |              |         |
| <20            | 316 2                | 317 2                    | NA   | NA           | NA      |
| 20-40          | 2321 7               | 2313 2                   | 3.489| 0.725-16.794| 0.119   |
| 40-65          | 4044 22              | 4045 11                  | 1.946| 0.943-4.013  | 0.072   |
| ≥65            | 1356 5               | 1362 1                   | 4.995| 0.584-42.755| 0.142   |
| **Gender**     |                      |                          |      |              |         |
| Female         | 3568 19              | 3566 8                   | 2.345| 1.026-5.357  | 0.043   |
| Male           | 4469 15              | 4471 8                   | 1.828| 0.775-4.312  | 0.168   |
| **Hypertension** |                    |                          |      |              |         |
| No             | 6103 27              | 6102 11                  | 2.440| 1.210-4.919  | 0.013   |
| Yes            | 1934 7               | 1935 5                   | 1.328| 0.421-4.193  | 0.629   |
| **Hyperlipidemia** |                |                          |      |              |         |
| No             | 7093 26              | 7097 14                  | 1.834| 0.958-3.513  | 0.067   |
| Yes            | 944 8                | 940 2                    | 3.952| 0.838-18.648 | 0.083   |
| **CCI**        |                      |                          |      |              |         |
| 0              | 5169 21              | 5155 11                  | 1.915| 0.923-3.972  | 0.081   |
| ≥1             | 2868 13              | 2882 5                   | 2.498| 0.890-7.012  | 0.082   |

‡Adjust for variables, including age, gender, and comorbidity.

aModels adjusted for gender and Charlson comorbidity index.

bModels adjusted for age, hypertension, hyperlipidemia and Charlson comorbidity index.

cModels adjusted for age, gender, hyperlipidemia and Charlson comorbidity index.

dModels adjusted for age, gender, hypertension and Charlson comorbidity index.

eModels adjusted for age, gender, hypertension and hyperlipidemia.

NA: not applicable.