G Model
HAZMAT-14440; No. of Pages 8

ARTICLE IN PRESS

Journal of Hazardous Materials xxx (2012) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Journal of Hazardous Materials

journal homepage: www.elsevier.com/locate/jhazmat

BMI-based approach reveals direct impact of metal dust exposure on influenza-associated lung function decrement risk in smelters

Yi-Hsien Cheng, Chung-Min Liao*

Department of Bioenvironmental Systems Engineering, National Taiwan University, Taipei 10617, Taiwan, ROC

HIGHLIGHTS

- ► Metal exposure affects flu-associated lung function decrement risk in smelters.
- ► A BMI-flu-metal-lung hazard association is constructed.
- ► Smelters should be aware of severe weight gains.

ARTICLE INFO

Article history:
Received 7 February 2012
Received in revised form 16 July 2012
Accepted 22 July 2012
Available online xxx

Keywords:
Metal dust
Influenza
Lung function
Smelters
Body mass index (BMI)
Risk assessment

ABSTRACT

Metal dust exposure strongly affects human health, especially for smelters. Little is known, however, about the impact of metal dust exposure on influenza-associated lung function decrement risk in smelters. Different body mass index (BMI) groups were also associated with respiratory diseases. The purpose of this study was to use a probabilistic risk assessment approach to explicitly link occupational metal dust exposure, BMI-correlated health effects, and influenza-associated lung function decrements to investigate potential risk among smelters. Here we showed that (i) influenza A-associated metal dust exposure in SiMn/FeMn/FeCr smelters had slightly higher health risks than that in FeSi/Si-metal's, (ii) BMI $\geq$ 35 had the highest risk in respiratory infection exacerbations, and (iii) the estimated smelting metal dust induced forced expiratory volume in 1 s (FEV_1) decreasing rates were 0.59 and 1.11 $m^3\,mg^{-1}$ for FeSi/Si-metal and SiMn/FeMn/FeCr smelters, respectively. Our results suggested that smelters better be aware of severe weight gains (e.g., BMIs from 27–40) because it is likely to lead to 17–25% decrements in lung function. This study provides a novel probabilistic risk assessment framework to quantitatively assess the occupational health risk posed by metal dust exposure associated with influenza infection based on BMI measures.

1. Introduction

Numerous studies had been performed to associate metal dust exposure with respiratory diseases such as respiratory illness, chronic obstructive pulmonary disease (COPD), asthma, fibrosis, and even lung cancer as well [1,2]. Chen et al. [3] investigated the respiratory health in male Taiwanese steelworkers given occupational dust exposure, indicating that higher cumulative respirable dust concentration ($\geq$2 mg yr m^{-3}) would lead to higher prevalence in respiratory symptoms including cough frequently (12.7%), phlegm frequently (14.7%), wheezing (4.3%), and breathlessness (9.4%) and lower FVC (forced vital capacity) of 3.87 L.

On the other hand, different body mass index (BMI) groups were associated with respiratory diseases such as COPD, asthma, and pneumonia [4–8]. BMI is a global measurement of one's thinness or fatness assessed by the weight in kilograms divided by square of the height in meters that is age-independent and the same for both genders. Chinn et al. [4] investigated the alterations in lung function of 1,005 male shipyard workers during the averaged observation time of 6.9 years, revealing that 1 kg increment in body mass would contribute to a mean reduction in FEV_1 (forced expiratory volume in 1 second) and FVC by 17.6 and 21.1 mL, respectively. Chen et al. [5] conducted a study containing 1202 adults and observed the similar results in weight gain-specific change in FEV_1 and FVC. They also indicated that each gain in BMI would give rise to excess loss in FVC and FEV_1, respectively, by 61 and 57 mL for males.

Kornum et al. [7] investigated the association between BMI and pneumonia, indicating that among male participants with low BMI (BMI $\leq$ 22.5) and moderately high BMI (30.0 $\leq$ BMI $\leq$ 34.9) had nearly the same adjusted hazard ratio for pneumonia of 1.4 (95% CI: 1.1–1.7) and 1.4 (1.2–1.7), respectively. Similar trend was observed in male participants at the lowest BMI (BMI $\leq$ 22.0) and highest

* Corresponding author. Tel.: +886 2 2363 4512; fax: +886 2 2362 6433.
E-mail addresses: cmliao@ntu.edu.tw, cmliao@ccms.ntu.edu.tw (C.-M. Liao).

0304-3894/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jhazmat.2012.07.043

Please cite this article in press as: Y.-H. Cheng, C.-M. Liao, BMI-based approach reveals direct impact of metal dust exposure on influenza-associated lung function decrement risk in smelters, J. Hazard. Mater. (2012), http://dx.doi.org/10.1016/j.jhazmat.2012.07.043

BMI category (BMI ≥ 30.0) in the study associating both BMI and asthma prevalence, giving the adjusted odds ratio of 3.05 (95% CI: 1.37–6.78) and 2.92 (1.39–6.14), respectively [8].

The above mentioned studies rarely consider the occupational metal dust exposure, BMI-correlated health effects, and lung function decrements simultaneously. Yet, there is a lack of dose-response profile describing well the relationship between metal dust exposure concentration and lung function alterations. Fortunately, Johnsen et al. [9] first conducted a longitudinal study to construct the dose-response relationship between metal dust exposure and annual FEV_1 decline, indicating that increasing in metal dust exposure and exposure duration would both accelerate the FEV_1 decline.

Prior to the outbreak of pandemic H1N1 2009, obesity had not been considered as a risk factor for severe influenza morbidity [10,11]. Díaz et al. [11] investigated patients in the intensive care unit (ICU) in Spain and found that obese patients compared to non-obese ones had longer ICU length of stay of 13.7 ± 11.7 days and longer mechanical ventilation remaining of 9.3 ± 9.7 days. Smith et al. [12] suggested that obese mice may have higher risk in influenza complications compared to lean ones. A recent study [7] also indicated that subsequent hospitalization with pneumonia was associated with obesity.

Occupational metal dust exposure-correlated, influenza infection-associated, and BMI group-specific health risks are the prevalent issues nowadays. Long-term metal dust exposure and pulmonary function decrement risk exists in metallic workers as well as the pulmonary exacerbation risk exists in influenza virus infectors. Nevertheless, the mechanistic and quantitative linkages among metal dust exposure, influenza infection, and pulmonary function in different BMIs are still obscure and lack of available epidemiological data. Moreover, appropriate BMI cutoffs are needed to better assess the BMI-related health risks.

Therefore, the purpose of this present study was to examine the above mentioned health-related outcomes through linking both mechanistic and stochastic models in a probabilistic risk point of view to better assess the impact of chronic metal dust exposure on influenza infection-associated lung function decrement risk in smelters based on a BMI measure.

2. Materials and methods

2.1. Study data

We first reanalyzed and associated the experimental data of respiratory symptoms scores (RSS) and FEV_1 dynamics of influenza infection provided by Hayden et al. [13] and Kondo and Abe [14], respectively. Two valuable longitudinal data performed by Chen et al. [5] and Johnsen et al. [9] were adopted for providing us a chance to look into the relationships between BMI and lung functions and between specific metal dust exposure levels and lung function decrements. All the adopted epidemiological data were listed in Table 1.

Hayden et al. [13] investigated 19 normal volunteers intranasally inoculated with influenza virus A/Texas/36/91(H1N1) by a median concentration of 10^5 TCID50 mL^{-1} (TCID50 was measured as 50% tissue culture infective dose) and observed viral load and RSS varied with days post infection. In their study, a four-point (0–3 representing absent to severe) symptom assessment was applied twice a day. They found that on day 2 post infection, the viral load and RSS reached peak then went down. The average scores for upper and lower respiratory symptoms on day 2 post infection were 3 and 0.44, respectively. Among 19 volunteers, 14 (74%) were females and aged 21 years old in median (ranging from 19–40 yr).

Kondo and Abe [14] examined the lung function data of 20 asthmatic children aged 8 to 12 years before and after influenza infection during the epidemics in the period 1978–1985. Decrement in FEV_1 of more than 20% from baseline value was considered significant. Based on the described principle, 15 of 20 children were considered significant. Among 15 children, 8 were infected by influenza A where the other 7 were infected by influenza B. On the second day after influenza infection, decreased FEV_1 for total, influenza A and B reached maximum values (Mean ± SD) of 30.3 ± 10.9, 28.9 ± 10.3, and 32.0 ± 12.2%, respectively, and gradually returned to normal levels of FEV_1 thereafter. No significant differences in the time course of FEV_1 in acute stage between influenza A and B infections were found.

Chen et al. [5] investigated longitudinal effects of change in body mass on measurements of ventilatory capacity. There were 703 follow-up data (3 data were excluded as outliers) in Humboldt in 1983 compared with the baseline data in 1977. The data were composed of 316 men and 387 women with the mean age of 41.5 and 42.5 years, and the mean BMI of 27.5 and 25.5 kg m^{-2}, respectively. Based on the results of multiple regression analysis adjusted for age, BMI at baseline, and smoking, each kg m^{-2} change in BMI would give rise to an average excess loss of 61 and 34 mL in FVC, 57 and 22 mL in FEV_1, and 69 and 3 mL s^{-1} in maximal midexpiratory flow rate (MMFR) for men and women, respectively.

Johnsen et al. [9] performed a 5-year prospective study of 2620 employees in 15 Norwegian smelters. The most important value of this study is that it was the first longitudinal study examining the dose-response relationship of specific metal dust exposure level and annual decline in lung function indices such as FEV_1 and FVC. Generally, the smelters can be grouped into two subgroups based on metal dust producing processes: (i) Ferrosilicon alloys (FeSi) and silicon metal (Si-metal), and (ii) silicon manganese (SiMn), ferromanganese (FeMn), and ferrochromium (FeCr). The larger production subgroup was FeSi/Si-metal smelters consisting of 11 smelters with 1697 employees, whereas the SiMn/FeMn/FeCr smelters consisted of 4 smelters with 923 employees. The time-weighted geometric mean (GM) of produced dust exposure concentration was 2.3 mg m^{-3} (10–90% percentiles: 0.03–5.60) in the FeSi/Si-metal smelters and 1.6 mg m^{-3} (0.02–2.30) in the SiMn/FeMn/FeCr smelters. For nonsmoker in FeSi/Si-metal smelters, the corresponding annual decline in FVC and FEV_1 were 36.4 and 24.7, 27.6 and 17.1, and 44.4 and 35.8 mL at lower, middle, and upper tertile of dust exposure concentration, respectively. On the other hand, in SiMn/FeMn/FeCr smelters, the corresponding annual decline in FVC and FEV_1 were 29.2 and 29.9, 29.6 and 34.3, and 44.8 and 35.8 mL at lower, middle, and upper tertile of dust exposure concentration, respectively.

2.2. Dose-response analysis

In this study, the dose-response relationships included four phases: (i) BMI-specific alterations in FEV_1, (ii) smelting metal induced lung function decrements in smelters, (iii) influenza infection associated FEV_1 and RSS exacerbations, and (iv) smelting metal-specific RSS exacerbations based on influenza infection in various BMI groups.

In the first phase, the regression data of the relationship between BMI and FEV_1 were adopted from Chen et al. [5]. For the obese and overweight groups, each kg m^{-2} gain in BMI from baseline (normal-weight group) would give rise to an excess loss in FEV_1 of 57 mL for men; whereas for underweight group, this assumption was made oppositely. The normally distributed non-linear fitting curve was used to describe the relationship between BMI and FEV_1. Here we defined the range of BMI ≤ 18.5, 18.5 ≤ BMI ≤ 24, 24 ≤ BMI ≤ 27, and BMI ≥ 27 kg m^{-2} as underweight (UW), normal-weight (NW), overweight (OW), and obese (OB) groups, respectively [15]. Noticeably,

Table 1
Adopted epidemiological raw data describing day post infection-specific % FEV_1 decrement and respiratory symptoms scores and the dose-response relationship between metal dust exposure and FEV_1 decrement.

Days post infection (DPI)	FEV_1 decrement (%)	Respiratory symptoms scores (–)[a]	Metal dust concentration ($mg\,m^{-3}$)[b]
Influenza			
0	7.7 ± 6.6[c]	0.11	–
1	18.4 ± 10.7	0.21	–
2	28.9 ± 10.3	0.57	–
3	26.4 ± 10.3	0.54	–
4	12.0 ± 6.1	0.48	–
5	22.5 ± 13.4	0.34	–
6	18.3 ± 11.8	0.22	–
7	13.3 ± 12.3	0.15	–
8	10.9 ± 15.5	0.11	–
FeSi/Si-metal smelters			
–	0.69 (0.54–0.84)[d]	–	1.65
–	0.48 (0.27–0.68)	–	2.30
–	1.00 (0.80–1.20)	–	3.05
SiMn/FeMn/FeCr smelters			
–	0.83 (0.64–1.02)	–	1.41
–	0.96 (0.69–1.23)	–	1.60
–	1.00 (0.80–1.20)	–	1.79

[a] Adopted and normalized from Hayden et al. [13]. Respiratory symptoms scores (RSS) represents the summation of upper and lower RSS where a score of 1 corresponds to the maximum reported score value.
[b] Adopted from Johnsen et al. [9] where the median concentrations were 2.30 (80% CI: 0.03–5.60) and 1.60 (0.02–2.30) $mg\,m^{-3}$ for FeSi/Si-metal and SiMn/FeMn/FeCr smelters, respectively.
[c] Mean ± SD. Adopted from Kondo and Abe [14].
[d] Median with 95% CI. Adopted from Johnsen et al. [9] and transferred into % FEV_1 decrement based on predicted FEV_1 of 3.587 L for 40-year-old males with 1.70 m in height calculated from the equation: $FEV_1 = -1.44 - 0.032\,\text{Age} + 3.71\,\text{Height}$ [28].

the ranges of BMI in obese group were further divided as obese 1 (OB1, $27 \le \text{BMI} \le 30$), obese 2 (OB2, $30 \le \text{BMI} \le 35$), and obese 3 (OB3, $\text{BMI} \ge 35$).

In the second phase, smelting metal particle induced FEV_1 decrements were examined among smelters with different BMIs based on an one-year metal dust exposure scenario by incorporating the above derived relationship of BMI-specific change in FEV_1. The concentration probability distribution profiles of both FeSi/Si-metal and SiMn/FeMn/FeCr smelters were reconstructed followed by Johnsen et al. [9]. Here we assumed that metal-related FEV_1 reducing patterns within each segment in the level of smelting metal were stationary [16]. Therefore, a homogeneous Poisson process can be applied to quantify the metal induced FEV_1 reducing rates of both smelters,

$$FEV_{1,c} = \alpha_c \mu_c \exp(\mu_c C), \quad (1)$$

where C is the concentrations of the smelting metal dust ($mg\,m^{-3}$), $FEV_{1,c}$ is the smelting metal induced FEV_1 decrements (mL), α_c is the parameter representing the area under the curve of the FEV_1–C profile ($mg\,m^{-3}\,mL$), and μ_c is the parameter describing the metal-associated FEV_1 reducing rate ($m^3\,mg^{-1}$).

In the third phase, by incorporating both human experimental data of FEV_1 and RSS varied with day post influenza infection adopted from Kondo and Abe [14] and Hayden et al. [13], respectively, a dose-response relationship could be constructed. A biologically-based 4-parameter Hill equation was used to link the relationship between influenza A-associated RSS and FEV_1,

$$\text{RSS} = \frac{(\text{RSS}_{max} - \text{RSS}_{min}) \times (\text{RFEV}_{1,50})^n}{(\%\text{FEV}_1)^n + (\text{RFEV}_{1,50})^n} + \text{RSS}_{min}, \quad (2)$$

where RSS_{max} and RSS_{min} are the maximum and minimum responses of RSS given change in $\%\text{FEV}_1$, $RFEV_{1,50}$ is the half maximal effective $\%\text{FEV}_1$ causing 50% response of RSS, and n is the Hill coefficient.

For the last phase, the Hill based dose-response relationship of % predicted FEV_1 and corresponding RSS was linked by the relationship of smelting metal particle concentration associated FEV_1 decrements to estimate the RSS conditional probability expressing as $P(\text{RSS}|C)$ for various BMI groups as a result of smelting metal exposure and influenza A virus infection.

2.3. Probabilistic risk assessment

This study implemented a probabilistic risk assessment approach to assess the potential exacerbations risk of RSS resulted from long-term smelting metal particle exposure and influenza A virus infection at particular change of BMI. The exacerbations risk at specific smelting metal particle concentration-related respiratory symptoms scores for different BMI groups can be obtained as probability density function (pdf) of smelting metal concentration ($P(C)$) multiplied with the conditional probability of $P(\text{RSS}|C)$. As a result, a joint probability function could be applied to estimate the risk probability and described as,

$$P(R_{\text{RSS}(C)}) = P(C) \times P(\text{RSS}|C), \quad (3)$$

where $P\,(R_{\text{RSS}(C)})$ represents the estimated risk of smelting metal particle exposure and influenza A virus infection-associated RSS exacerbations within various BMI groups.

The study data were fitted with statistical models optimally selected on the basis of least squared criterion from a set of generalized linear and nonlinear autoregression models provided by TableCurve 2D packages (AISN Software Inc., Mapleton, OR, USA). A value of $p < 0.05$ was judged significant and coefficient of determination (r^2) represented the variance of data to the fitting model. The uncertainty and its impact on the expected risk estimate were quantified by a Monte Carlo (MC) simulation technique. A MC simulation was carried out with 10,000 iterations to assure the stability of those pdfs and generate 2.5- and 97.5-percentiles as the 95% confidence interval (CI) for all fitted models. The Crystal Ball® software (Version 2000.2, Decisioneering, Inc., Denver, Colorado, USA) was employed to implement the MC simulation.

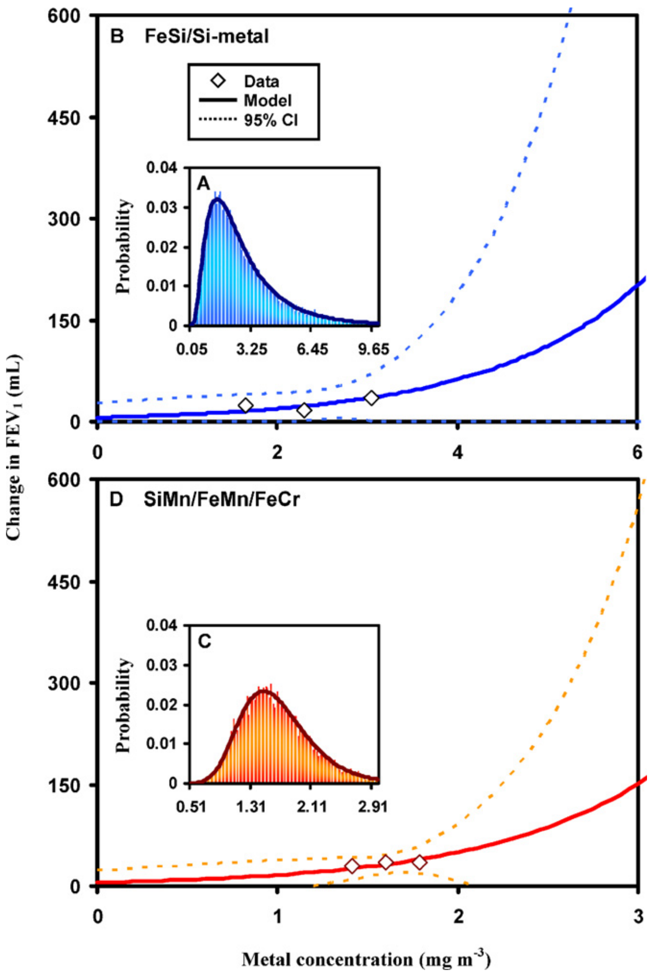

Fig. 1. Metal dust concentration distribution for smelters with (A) FeSi/Si-metal and (C) SiMn/FeMn/FeCr, respectively. (B) and (D) are the dose-response relationships between metal dust exposure and FEV_1 decrement described by a homogeneous Poisson process for FeSi/Si-metal and SiMn/FeMn/FeCr smelters, respectively.

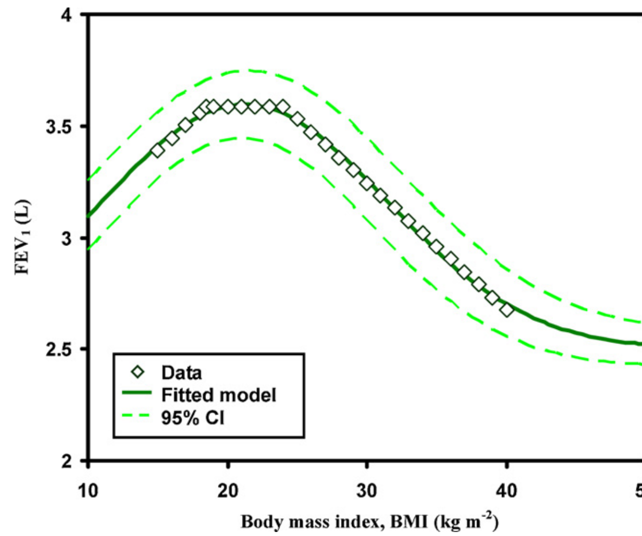

Fig. 2. BMI-specific FEV_1 profile described with a 4-parameter normally distributed fitting curve for UW, NW, OW, and OB groups.

3. Results

3.1. Metal exposure related lung function decrements with different BMIs

The lognormal (LN) model was found well to describe the smelting metal concentration distribution, resulting a geometric mean (gm) 2.30 mg m^{-3} and a geometric standard deviation (gsd) 2.00 for FeSi/Si-metal (Fig. 1A) and a gm 1.60 mg m^{-3} and a gsd 1.33 for SiMn/FeMn/FeCr smelters (Fig. 1C), respectively. Based on the metal concentration distribution profiles, 1st, 2nd and 3rd tertile were selected to assess the corresponding changes in FEV_1 as 1.65, 2.30, and 3.05 mg m^{-3} for FeSi/Si-metal smelters and 1.41, 1.60, and 1.79 mg m^{-3} for SiMn/FeMn/FeCr smelters.

A homogeneous Poisson process well described the relationship between smelting particle exposure level and change in FEV_1 for FeSi/Si-metal (Fig. 1B) and SiMn/FeMn/FeCr smelters (Fig. 1D). For FeSi/Si-metal smelters, the AUC constant (α_c) and the smelting metal particle induced FEV_1 decreasing rate (μ_c) were, respectively, estimated to be 9.96 mL mg m^{-3} and 0.59 m^3 mg^{-1} ($r^2 = 0.78$, $p = 0.12$), whereas for SiMn/FeMn/FeCr smelters, α_c and μ_c estimates were 4.91 mL mg m^{-3} and 1.11 m^3 mg^{-1}, respectively ($r^2 = 0.92$, $p < 0.05$).

Fig. 2 shows that a 4-parameter normally distributed fitting curve was found best describing the BMI-specific FEV_1 profile for the four BMI groups of UW, NW, OW, and OB ($r^2 = 0.99$, $p < 0.001$) followed the equation $a + b\exp(-0.5((x-c)/d)^2)$ with the four fitted parameters a, b, c, and d of 2.50 L, 1.10 L, 21.24 kg m^{-2}, and 10.19 kg m^{-2}, respectively. Our findings showed that the estimated percent predicted FEV_1 decreased from 95.05, 99.17, 95.76, and 90.84 to 34.52, 38.64, 35.23, and 30.30 for FeSi/Si-metal smelters at metal dust level of 10.05 mg m^{-3} (Fig. 3A) and to 20.15, 24.27, 20.86, and 15.93% for SiMn/FeMn/FeCr smelters at metal dust level of 5.60 mg m^{-3} (Fig. 3B), respectively, for UW, NW, OW, and OB1 groups.

3.2. Influenza infection-based respiratory illness and pulmonary effects

Fig. 4A shows the time-course of % decrements in FEV_1 and respiratory symptoms scores. The results indicated that both % predicted FEV_1 decrements and RSS started at day 0 post infection with the value of 7.7% and 0.11, peaked at day 2 post infection with the value of 28.9% and 0.57 then decreased to the value of 10.9% and 0.11 at day 8 post infection. Fig. 4B gives the averaged probability distribution of % FEV_1 decrement by considering all day post infection varied reduction in FEV_1 with the median of 17.1% (95% CI: 11.71–25.45). Fig. 4C shows the jointed dose-response relationship between percent predicted FEV_1 and RSS. This study discarded data on the 4th day (Fig. 4A) to better describe the fitted Hill dose-response relationship between % FEV_1 decrements as well as RSS as shown in Fig. 4B. Besides, Fig. 4A revealed the trend that both RSS and % FEV_1 decrements reached peak on the 2nd day and then return to background level gradually. The Hill equation well described the relationship between RSS and predicted FEV_1 ($r^2 = 0.98$, $p < 0.001$) with the fitted Hill coefficient (n) of 13.73, the maximum and minimum response RSS_{max} and RSS_{min} of 0.96 and 0.06, respectively, and the half maximal effective % FEV_1 causing 50% response of respiratory symptoms scores $RFEV_{1,50}$ of 73.24% predicted FEV_1.

3.3. BMI-varied influenza infection-based respiratory illness exacerbations

By incorporating Hill-based relationship between % predicted FEV_1 and RSS, BMI-varied influenza infection associated RSS exacerbations in smelters could thus be explored and quantified (Fig. 5). For FeSi/Si-metal smelters, the maximum RSS based on influenza infection and smelting metal exposure was first reached by OB3

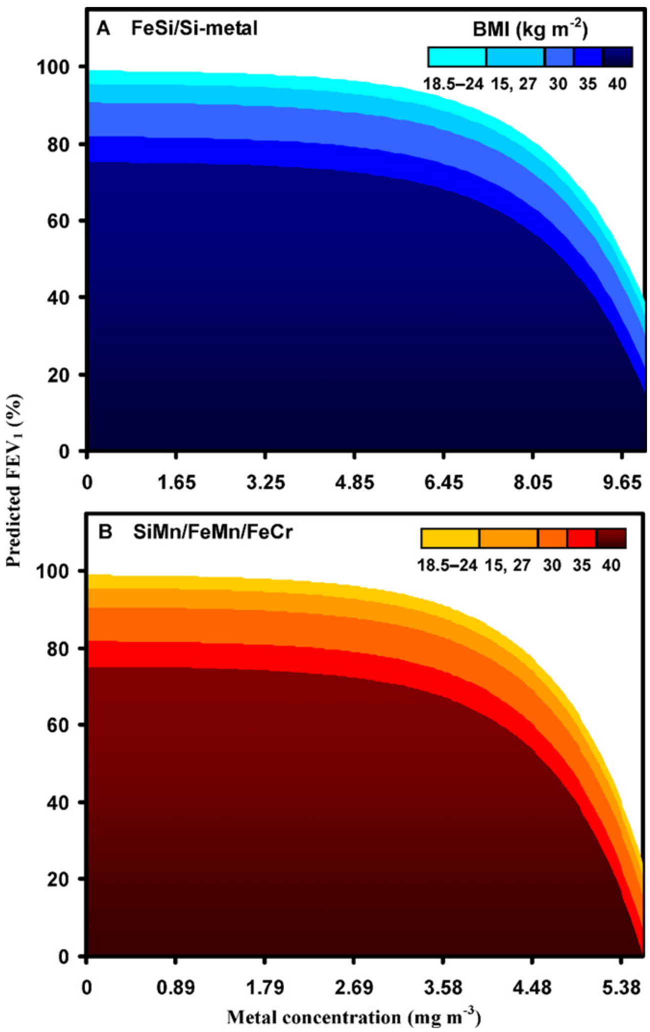

Fig. 3. Metal dust exposure induced FEV_1 decrement within different BMIs for (A) FeSi/Si-metal and (B) SiMn/FeMn/FeCr smelters, respectively. Where the darkest area represents the OB3 group followed by OB2, OB1, UW and OW groups, and the lightest area represents the NW group.

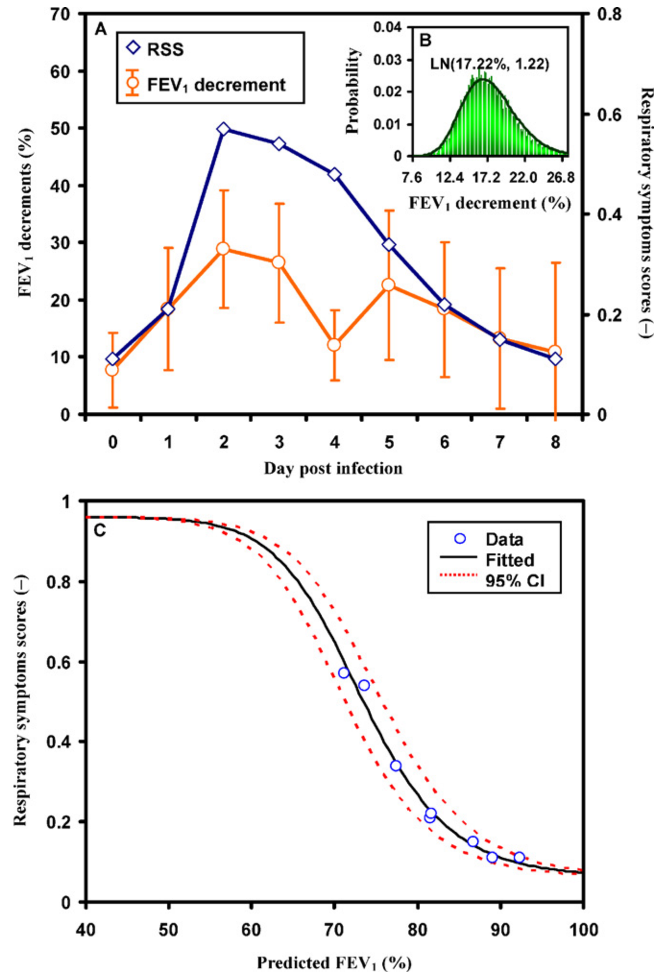

Fig. 4. (A) Day post infection varied FEV_1 decrement and RSS adopted from Kondo and Abe [14] and Hayden et al. [13], respectively. (B) Probability distribution of FEV_1 decrement of influenza infected cases. (C) Dose-response relationship between % predicted FEV_1 and RSS described by a 4-parameter Hill equation.

followed by OB2, OB1, OW and UW, and NW at exposure concentration of 8.95, 9.35, 9.65, 9.85, and 9.95 mg m^{-3}, respectively (Fig. 5A). On the other hand, for SiMn/FeMn/FeCr smelters, the maximum RSS was reached first by OB3 followed by OB2, OB1, OW and UW, and NW given exposure concentration at 4.83, 5.00, 5.20, 5.28, and 5.35 mg m^{-3}, respectively (Fig. 5B). The starting points of RSS based on various BMI groups were 0.33, 0.22, 0.31, 0.49, 0.82, and 0.92, respectively, for UW, NW, OW, OB1, OB2, and OB3.

3.4. Respiratory illness exacerbations risk estimates

Fig. 6 shows the synoptic estimated risk profile at both FeSi/Si-metal and SiMn/FeMn/FeCr smelters for different BMI groups. The exceedance risk (ER) profile could be constructed by linking both concentration probability distribution of smelting metal (Fig. 1A and B) and RSS exacerbations profile given influenza infection and smelting metal particle exposure (Fig. 5). At particular ER, for instance, ER = 0.5 (ER0.5), the RSS exacerbations were much greater for OB3 followed by OB2, OB1, UW, OW, and NW for both smelters.

Here the minimum and maximum RSS (RSS_{min}–RSS_{max}) were used to represent the potential exacerbations risk of change in BMI given smelting metal particle exposure and influenza infection (Table 2). We found that greater change in BMI would lead to greater RSS exacerbations risk. For both smelters, the maximum RSS at ER0.9 and ER0.5 were almost the same for each BMI group. For FeSi/Si-metal smelters at ER0.1, we found slightly lesser differences in RSS change for the obese subgroups: OB1 (0.44–0.64), OB2 (0.64–0.89), and OB3 (0.89–0.94) compared to that of obese subgroups in SiMn/FeMn/FeCr smelters: OB1 (0.37–0.57), OB2 (0.57–0.86), and OB3 (0.86–0.94). Even in the worst case as for the OB3 group, it is unlikely that lung function decrement would exceed 45% for FeSi/Si-metal smelters, suggesting acceptable health effects (Table 2). Fig. 7 reveals the exacerbations risks of FEV_1 decrement and RSS at ER0.1 for both smelters given metal dust exposure and influenza infection. A J-shaped probabilistic risk profile of FEV_1 decrement ($dFEV_1$) and RSS exacerbations can be observed (Fig. 7).

4. Discussion

4.1. Exposure-effect health risk estimates

This study reconstructed the dose-response relationship between metal dust exposure level and lung function impairment for smelters. Simulated results revealed that given the same metal dust exposure concentration, FEV_1 decrements were nearly twice for SiMn/FeMn/FeCr smelters than that for FeSi/Si-metal smelters. The steeper declines in FEV_1 in smelters exposed to

Table 2
Influenza infection associated FEV_1 decrement and respiratory symptoms scores (RSS) exacerbations risks in BMI-specific smelters varied with exceedance risks at 0.9, 0.5, and 0.1.

BMI (kg m^{-2})	FeSi/Si-metal smelters			SiMn/FeMn/FeCr smelters		
	0.9	0.5	0.1	0.9	0.5	0.1
	FEV_1 decrement (%)					
15–18.5	18.2–22.3[a]	18.5–22.7	21.5–25.6	18.4–22.6	18.8–22.9	19.7–23.9
18.5–24	17.1–18.2	17.4–18.5	20.4–21.5	17.3–18.4	17.7–18.8	18.6–19.7
24–27	18.2–21.6	18.5–22.0	21.5–24.9	18.4–21.8	18.8–22.2	19.7–23.2
27–30	21.6–26.6	22.0–26.9	24.9–29.9	21.8–26.8	22.2–27.1	23.2–28.1
30–35	26.6–35.4	26.9–35.7	29.9–38.7	26.8–35.6	27.1–36.0	28.1–36.9
35–40	35.4–42.1	35.7–42.4	38.7–45.4	35.6–42.3	36.0–42.7	36.9–43.6
	RSS					
15–18.5	0.22–0.34	0.23–0.35	0.31–0.46	0.23–0.35	0.24–0.36	0.26–0.39
18.5–24	0.20–0.22	0.21–0.23	0.28–0.31	0.20–0.23	0.21–0.24	0.23–0.26
24–27	0.22–0.32	0.23–0.33	0.31–0.44	0.23–0.32	0.24–0.33	0.26–0.37
27–30	0.32–0.50	0.33–0.52	0.44–0.64	0.32–0.51	0.33–0.53	0.37–0.57
30–35	0.50–0.82	0.52–0.83	0.64–0.89	0.51–0.83	0.53–0.84	0.57–0.86
35–40	0.82–0.93	0.83–0.93	0.89–0.94	0.83–0.93	0.84–0.93	0.86–0.94

[a] Min–max.

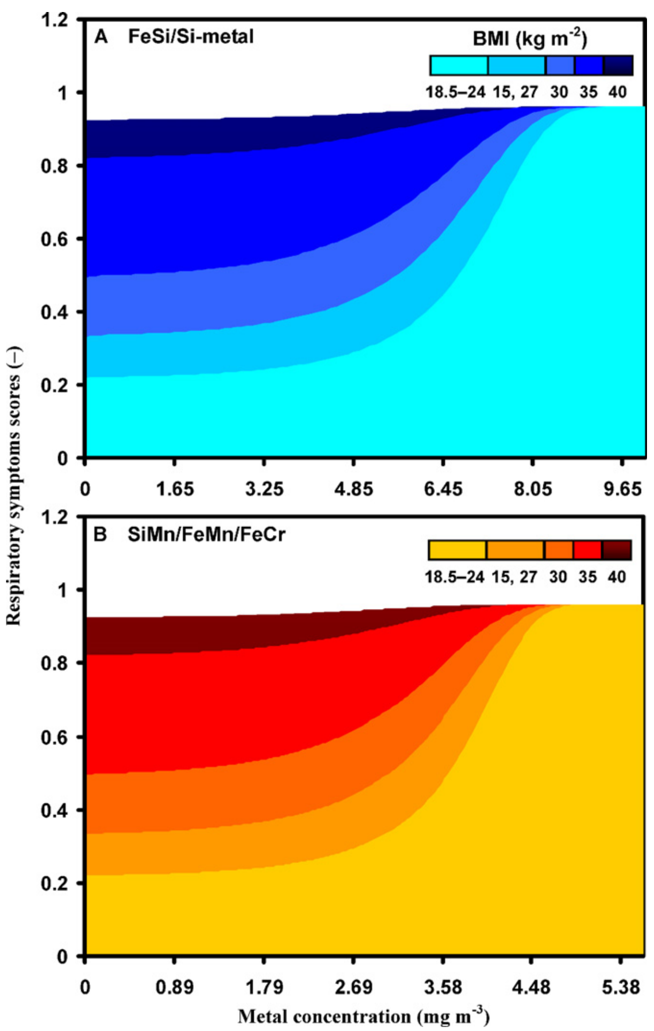

Fig. 5. Metal dust exposure and influenza infection-associated RSS exacerbations for different BMIs of (A) FeSi/Si-metal and (B) SiMn/FeMn/FeCr smelters, respectively. The lightest and darkest area represent, respectively, the NW and OB3 groups.

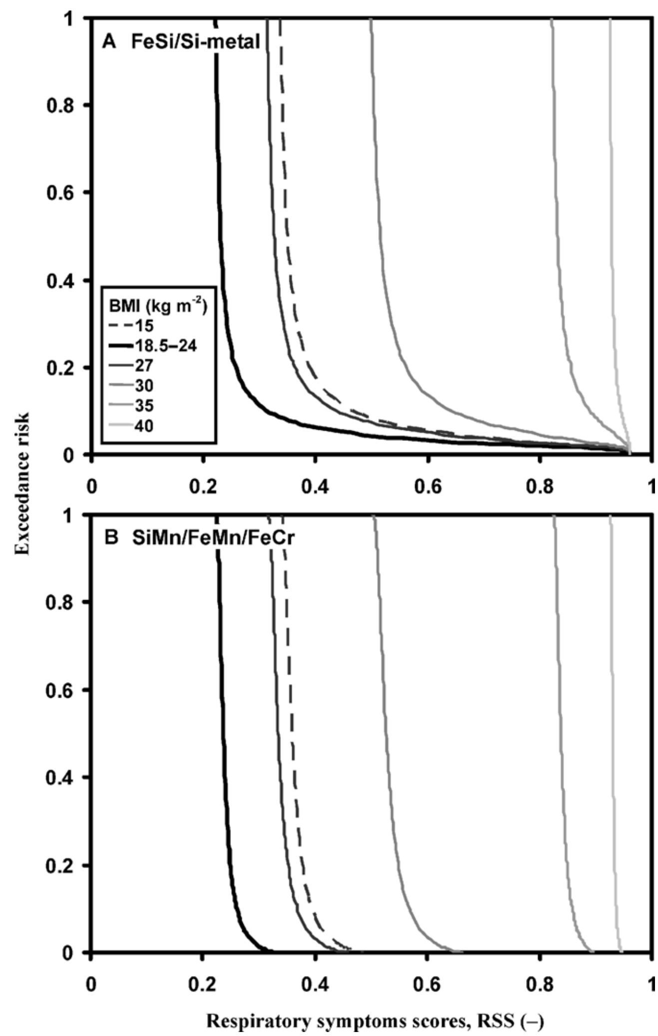

Fig. 6. BMI-specific probabilistic risk profile of RSS exacerbations given metal dust exposure and influenza infection for (A) FeSi/Si-metal and (B) SiMn/FeMn/FeCr smelters, respectively.

SiMn/FeMn/FeCr metal dusts may due to the more harmful exposure to the airways [9].

The exposure limits assessed by time-weighted averages suggested by NIOSH (National Institute for Occupational Safety and Health) and by OSHA (Occupational Safety and Health Administration) for silicon dust, manganese and chromium metal dust were 5, 1, and 0.5 mg m^{-3} and 5, 5, and 1 mg m^{-3}, respectively [17]. Some of the metal dust concentration distributions fell beyond the permitted exposure level recommended by NIOSH and OSHA,

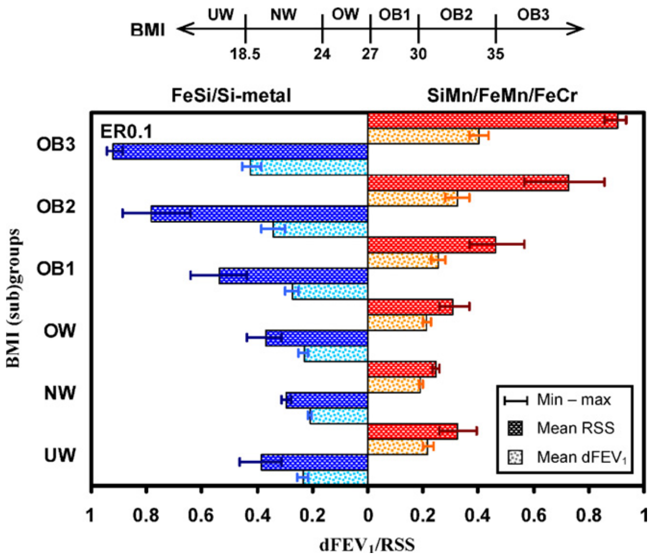

Fig. 7. Influenza infection associated FEV_1 decrement and RSS exacerbations risks in BMI-specific smelters with exceedance risks at 0.1 for UW, NW, OW, OB1, OB2, and OB3 groups where the left- and right-hand sides represent FeSi/Si-metal and SiMn/FeMn/FeCr smelters, respectively.

which may lead to higher lung function decrement risks among smelters.

Numerous studies had supported the idea that lung function impairment is highly correlated with duration of employment, previous exposure, size and concentration of metal dust, and the constituent in metal dust as well [3,18]. Long-term exposure to metal dust is associated with either COPD or asthma [19,20]. Based on 1-year exposure scenario, considering the health risk caused by metal dust exposure and BMI solely, OB3 group had the highest chance to develop COPD or asthma ($\leq$80% predicted FEV_1), whereas for smelters with influenza infection, all BMI groups had the chance developing COPD or asthma.

In this study, metal dust exposure and influenza infection-associated RSS exacerbations risks were found highest for severe obese group (i.e., OB3) followed by OB2, OB1, UW, OW, and NW for both FeSi/Si-metal and SiMn/FeMn/FeCr smelters. This is not surprising since BMI-specific FEV_1 estimates were found highest of 3.56–3.60 L for NW, followed by OW, UW, and OB with the estimates of 3.44–3.56, 3.41–3.56, and 2.70–3.44 L, respectively. Here a normally distributed dose-response profile was assumed and used to describe the relationship between BMI and FEV_1. Ubilla et al. [21] indicated that both low (BMI < 20) and high BMI groups (BMI > 30) were associated with poor FEV_1 and FVC in adulthood. Ubilla et al. [21] further indicated fatness may be moderate at lower BMI, therefore, increments in BMI may increase muscle and thus enhance lung function, but beyond certain level of BMI (i.e., BMI $\geq$ 30) in that the increment is due partly to the adipose tissue increase and lung function exacerbations.

A J-shaped risk profile was observed in BMI-varied FEV_1 decrements and RSS exacerbations similar to the association between BMI and mortality proposed by Jee et al. [22] (i.e., the dose-response profile is asymmetric and that higher BMI end such as obese group would have higher mortality than that in the lower end of BMI such as underweight group). However, an U-shaped BMI-specific mortality risk profile (i.e., BMI-associated mortality profile is symmetric and both higher and lower BMI ends would have similar mortalities) was observed for East Asians as well as North Americans and Europeans [23,24].

4.2. Limitations and implications

A normal distribution response profile was chosen to describe the relationship among FEV_1 and different BMIs due to the existed data gap for further estimation of FEV_1 at lower BMIs for UW group. However, normally distributed response profile may underestimate the risks for UW group given a U-shaped association. The estimated predicted FEV_1s were dependent on age and height; nevertheless, the relationship was constructed mainly based on Caucasian data. Future studies may need to focus more on building up the predicted FEV_1 profile for Asians to better assess the corresponding health risks in Asian countries. In this study, influenza infection related exacerbated risks were estimated apart from metal dust exposure which may cause overestimate of total health risks. Nevertheless, there is a lack of available epidemiological data quantifying the pulmonary function decrement risks given metal dust exposure and influenza infection for BMI-specific metallic industrial workers simultaneously.

Long-term exposure induced lung function exacerbations risks among metallic workers worth further studying by taking into account other health effects caused by smoking, alcohol drinking or chronic respiratory diseases [3,25]. Type of metal dust inhaled is the issue of main concern as well as the quantification of accumulated internal doses in different regions of respiratory tract. Human respiratory tract (HRT) model can be applied to quantify the size-specific number concentration of metal dust deposited in each respiratory compartment based on the principle of mass balance [26]. Whereas physiologically based pharmacokinetic (PBPK) model can be used to simulate the kinetics of inhaled metal dusts by means of considering compartments such as lung, liver, kidney, blood, tissues, and etc. [27]. With more detailed experimental and monitoring data inputs, both HRT and PBPK models can be simultaneously applied to construct internal size-specific dose-response relationships for better occupational health risk assessments.

5. Conclusions

The following main conclusions can be drawn: (i) SiMn/FeMn/FeCr smelters had slightly higher health risks than that for FeSi/Si-metal smelters given metal dust exposure and influenza infection, (ii) OB3 group had the highest risk in RSS exacerbations followed by OB2, OB1, UW, OW, and NW groups, and (iii) a J-shaped probabilistic risk profile can be observed. Based on our estimations, smelters should be aware of severe weight gains, say BMI alters from 27 to 40 or more as well as influenza infection since both aspects could lead to 25 and 17% decrement in FEV_1, respectively. Overall, this study provides a novel probabilistic risk assessment framework to better assess occupational health risk given metal dust exposure and influenza infection based on BMI measures.

Acknowledgement

The authors acknowledge the financial support of the National Science Council of Republic of China under Grant NSC 100-2313-B-002-012-MY3.

References

[1] L.M. Bradshaw, D. Fishwick, T. Slater, N. Pearce, Chronic bronchitis, work related respiratory symptoms, and pulmonary function in welders in New Zealand, Occup. Environ. Med. 55 (1998) 150–154.
[2] A. Blair, P. Stewart, J.H. Lubin, F. Forastiere, Methodological issues regarding confounding and exposure misclassification in epidemiological studies of occupational exposures, Am. J. Ind. Med. 50 (2007) 199–207.
[3] P.C. Chen, P.E. Doyle, J.D. Wang, Respirable dust exposure and respiratory health in male Taiwanese steelworkers, Ind. Health 44 (2006) 190–199.

[4] D.J. Chinn, J.E. Cotes, J.W. Reed, Longitudinal effects of change in body mass on measurements of ventilatory capacity, Thorax 51 (1996) 699–704.
[5] Y. Chen, S.L. Horne, J.A. Dosman, Body weight and weight gain related to pulmonary function decline in adults: a six year follow up study, Thorax 48 (1993) 375–380.
[6] D.M. Mannino, A.S. Buist, T.L. Petty, P.L. Enright, S.C. Redd, Lung function and mortality in the United States: data from the First National Health and Nutritional Examination Survey follow up study, Thorax 58 (2003) 388–393.
[7] J.B. Kornum, M. Nørgaard, C. Dethlefsen, K.M. Due, R.W. Thomsen, A. Tjønneland, H.T. Sørensen, K. Overvad, Obesity and risk of subsequent hospitalisation with pneumonia, Eur. Respir. J. 36 (2010) 1330–1336.
[8] E. Luder, R.I. Ehrlich, W.Y.W. Lou, T.A. Melnik, M. Kattan, Body mass index and the risk of asthma in adults, Respir. Med. 98 (2004) 29–37.
[9] H.L. Johnsen, S.M. Hetland, J. Šaltyte Benth, J. Kongerud, V. Søyseth, Dust exposure assessed by a job exposure matrix is associated with increased annual decline in FEV_1: a 5-year prospective study of employees in Norwegian smelters, Am. J. Respir. Crit. Care Med. 181 (2010) 1234–1240.
[10] O.W. Morgan, A. Bramley, A. Fowlkes, D.S. Freedman, T.H. Taylor, P. Gargiullo, B. Belay, S. Jain, C. Cox, L. Kamimoto, A. Fiore, L. Finelli, S.J. Olsen, A.M. Fry, Morbid obesity as a risk factor for hospitalization and death due to 2009 pandemic influenza A(H1N1) disease, PLoS ONE 5 (2010) e9694.
[11] E. Díaz, A. Rodríguez, I. Martin-Loeches, L. Lorente, M. Martín, J.C. Pozo, J.C. Montejo, A. Estella, Á. Arenzana, J. Rello, H1N1 SEMICYUC Working Group, Impact of obesity in patients infected with 2009 influenza A(H1N1), Chest 139 (2011) 382–386.
[12] A.G. Smith, P.A. Sheridan, R.J. Tseng, J.F. Sheridan, M.A. Beck, Selective impairment in dentritic cell function and altered antigen-specific $CD8^+$ T-cell responses in diet-induced obese mice infected with influenza virus, Immunology 126 (2009) 268–279.
[13] F.G. Hayden, R.S. Fritz, M.C. Lobo, W.G. Alvord, W. Strober, S.E. Straus, Local and systemic cytokine responses during experimental human influenza A virus infection: relation to symptom formation and host defense, J. Clin. Invest. 101 (1998) 643–649.
[14] S. Kondo, K. Abe, The effects of influenza virus infection on FEV_1 in asthmatic children: the time-course study, Chest 100 (1991) 1235–1238.
[15] Department of Health, Executive Yuan, R.O.C. (Taiwan DOH), Health Examination Online: Body Mass Index. Available at: http://health99.doh.gov.tw/onlinkhealth/onlink_bmi.aspx (accessed on 15.09.2011).
[16] H.M. Taylor, S. Karlin, An Introduction to Stochastic Modeling, Academic Press, Inc, San Diego, CA, 1994.
[17] Centers for Disease Control and Prevention (CDC), NIOSH Pocket Guide to Chemical Hazards, 2010. Available at: http://www.cdc.gov/niosh/npg/default.html (accessed on 5.01.2012).
[18] S.A. Meo, M.A. Azeem, M.M.F. Subhan, Lung function in Pakistani welding workers, J. Occup. Environ. Med. 45 (2003) 1068–1073.
[19] T.D. Levan, W.P. Koh, H.P. Lee, D. Koh, M.C. Yu, S.J. London, Vapor, dust, and smoke exposure in relation to adult-onset asthma and chronic respiratory symptoms: the Singapore Chinese health study, Am. J. Epidemiol. 163 (2006) 1118–1128.
[20] S. Weinmann, W.M. Vollmer, V. Breen, M. Heumann, E. Hnizdo, J. Vilinave, B. Doney, M. Graziani, M.A. McBurnie, A.S. Buist, COPD and occupational exposures: a case-control study, J. Occup. Environ. Med. 50 (2008) 561–569.
[21] C. Ubilla, P. Bustos, H. Amigo, M. Oyarzun, R.J. Rona, Nutritional status, especially body mass index, from birth to adulthood and lung function in young adulthood, Ann. Hum. Biol. 35 (2008) 322–333.
[22] S.H. Jee, J.W. Sull, J. Park, S.Y. Lee, H. Ohrr, G. Eliseo, J.M. Samet, Body-mass index and mortality in Korean men and women, N. Engl. J. Med. 355 (2006) 779–787.
[23] K.M. Flegal, B.I. Graubard, D.F. Williamson, M.H. Gail, Excess deaths associated with underweight, overweight, and obesity, JAMA 293 (2005) 1861–1867.
[24] D.F. Gu, J. He, X.F. Duan, K. Renolds, X.G. Wu, J. Chen, G.Y. Huang, C.S. Chen, P.K. Whelton, Body weight and mortality among men and women in China, JAMA 295 (2006) 776–783.
[25] H.L. Johnsen, V. Søyseth, S.M. Hetland, J. Šaltyte Benth, J. Kongerud, Production of silicon alloys is associated with respiratory symptoms among employees in Norwegian smelters, Int. Arch. Occup. Environ. Health 81 (2008) 451–459.
[26] J.W. Chen, C.M. Liao, S.C. Chen, Compartmental human respiratory tract modeling of airborne dust exposure from feeding in swine buildings, J. Air Waste Manag. Assoc. 54 (2004) 331–341.
[27] J.G. Teeguarden, J. Gearhart, H.J. Clewell III, T.R. Covington, A. Nong, M.E. Andersen, Pharmacokinetic modeling of manganese III: physiological approaches accounting for background and tracer kinetics, J. Toxicol. Environ. Health A 70 (2007) 1515–1526.
[28] J.E. Cotes, D.J. Chinn, M.R. Miller, Lung Function: Physiology, Measurement and Application in Medicine, sixth ed., Blackwell Publishing, Oxford, 2006.

Please cite this article in press as: Y.-H. Cheng, C.-M. Liao, BMI-based approach reveals direct impact of metal dust exposure on influenza-associated lung function decrement risk in smelters, J. Hazard. Mater. (2012), http://dx.doi.org/10.1016/j.jhazmat.2012.07.043