Associations between body mass index and the risk of mortality from lung cancer
A dose–response PRISMA-compliant meta-analysis of prospective cohort studies
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Abstract
Background: Whether body mass index (BMI) is associated with the risk of mortality from lung cancer (LC) is controversial, and the shape of dose–response relationship on this topic is not well-established. Thus, a dose–response meta-analysis was performed to clarify this association.

Methods: A search of PubMed and EMBASE was conducted, and 2-stage random-effect dose–response model was used to yield summary relative risks and its shape.

Results: Fifteen prospective cohort studies were eligible for inclusion criteria. The combined relative risks per 5 kg/m² in BMI for risk of LC mortality is 0.94 (95% confidence interval) 0.92–0.96), and nonlinear association was found (P nonlinearity < .0001), which indicated that compared with higher BMI, lower BMI showed higher LC mortality risk. Subgroup analyses revealed that this obesity paradox remained regardless of number of cases, follow-up duration, and study location, but this relationship was not observed among nonsmokers.

Conclusion: A nonlinear association between BMI and the risk of LC mortality was found, and higher BMI participants have a lower risk of LC death than slim people.

Abbreviations: BMI = body mass index, CI = confidence interval, LC = lung cancer, RR = relative risk.

Keywords: body mass index, dose–response meta-analysis, mortality from lung cancer

1. Introduction
In recent years, both developed and developing countries are confronted with common health problems, and overweight and obesity brought burden to 1 billion people.[11] Overweight and obesity are major risk factors regarding chronic diseases, including cancer and cardiovascular disease.[2–4] Lung cancer (LC) tops the list of all cancer mortality[5] among malignancies, and whether obesity is 1 of the risk factor for LC-associated mortality obtained research interest.[6–9] The relationship of obesity with the risk of LC mortality in previous studies showed inconsistency.[6,10] Some studies revealed a better prognosis among obese LC patients than normal-weight individuals.[8,9,11] Nevertheless, other researches illustrated both lower body mass index (BMI) and higher BMI increased the risk of mortality from LC.[12] Additionally, Dehal et al.[13] observed no association between obesity and the risk of LC mortality, which had been further verified in a prospective cohort study reporting that long-term annual change in BMI did not have an effect on the risk of mortality from LC.[14] A 2016 meta-analysis[6] conducted categorical analyses (eg, obesity vs normal weight) to clarify this association, which yielded an independent protective relationship between premorbid obesity and the risk of LC mortality, but mixed subjects with LC or not brought potential bias. Furthermore, several modifiers, such as sex,[2,3] smoking,[15,16] chronic obstructive pulmonary disease,[17] and asthma,[18] to some extent, affected results. Previous observational research frequently described the relationship of BMI with risk of cancer mortality as a U[19–21] or J shape in females[22]; however, limited sample size led to a lack of reliability of curve pattern.

So far, as we know, there is no available dose–response meta-analysis regarding this topic. Accordingly, the aims of this study were to reveal the relationship between BMI and the risk of mortality from LC, and to investigate precisely the shape of this association.

2. Methods
2.1. Ethics
Our study used previously published studies, and therefore, ethical approval was not necessary. In addition, all studies involved in our meta-analysis received ethics approval and patient consent was obtained.
2.2. Search strategy
This meta-analysis was conducted on the basis of PRISMA statement.\cite{23} An electronic literature search of PubMed and EMBASE databases was performed through January 2017, and the search strategy was illustrated in detail in Supplementary list S1 (http://links.lww.com/MD/B824). We performed a manual search of previous reference lists and reviews too. Unpublished reports had not attempted to identify.

2.3. Inclusion criteria
Two investigators independently selected the suitable publications according to the following inclusion criteria: exposure—BMI at least 3 quantitative categories; outcome—adjusted relative risk (RR) with 95% confidence interval (CI) on the relations of BMI and the risk of mortality of LC; additional data—the number of death cases and its total subjects or person-years; prospective cohort studies were included. Letters, conferences, references, and meta-analyses were excluded.

2.4. Data extraction and quality assessment
One investigator conducted data extraction, and then another investigator independently checked for accuracy. The following information was extracted: first author, publication year, study location, sample size, death cases, BMI categories, mean follow-up duration, LC assessment, BMI assessment, and maximally adjusted risk estimate with corresponding 95% CI and adjustment factors.

Two investigators assessed the quality of included research using the Newcastle-Ottawa quality assessment scale independently. After evaluating its 3 aspects (selection, comparability, and outcome), each study could be assigned 9 stars at most—9 stars (4 stars for selection; 3 stars for comparability; 2 stars for outcome). The quality of studies was ranked as low quality (below 3 stars), moderate quality (4–6 stars), and high quality (7–9 stars). Any conflicts on data extraction and quality assessment were solved by further discussion.

2.5. Data synthesis and statistical analysis
In this meta-analysis, RR with 95% CI were considered as common measures of the relationship between BMI and LC mortality risk, and a 2-stage dose-response meta-analysis was performed to assess this association. Firstly, the generalized least square regression described by Orsini et al\cite{24} was used to calculate the category-specific linear trend and 95% CIs for every 5 kg/m\(^2\) increase within each study from the natural logs of adjusted hazard ratios (HRs) and CIs across the categories of BMI. Secondly, the random-effects model\cite{25} was used to pool HRs and 95% CIs. This method requires additional data, such as the distribution of LC death cases, person-years, and RRs of each BMI categories. Person-years at every exposure level were often derived from follow-up duration and the number of participants when direct data were not reported. (And) We defined the mean or median of the quantitative categories as each exposure level, if not reported, the estimated midpoint was instead. Meanwhile, if lowest or highest boundaries were opened as cut-off values of BMI defined by WHO-recommended standard (eg, <18.5 kg/m\(^2\), 18.5–25 kg/m\(^2\), >30 kg/m\(^2\)), we set the extreme value as adjacent boundary value (eg, >25 kg/m\(^2\) considered as 30 kg/m\(^2\)).

The between-study heterogeneity was assessed by Q statistic ($P_{\text{heterogeneity}} < .10$, suggesting statistically significance) and the $I^2$ statistic\cite{26} (an $I^2$ of <50%, 50%–75%, or >75%, indicating low, moderate, or high heterogeneity, respectively). Potential nonlinear relationship between BMI and the risk of LC mortality was explored using restricted cubic splines, with 3 knots at percentiles 10%, 50%, and 90% of the distribution.\cite{27,28} A $P_{\text{nonlinearity}}$ value for curve linearity or nonlinearity was calculated by testing the null hypothesis that the estimated value of the second spline is equal to 0.\cite{28} Random-effects dose-response models using logarithms of RRs and CIs, the number of cases, and the number of participants across BMI categories were also performed assuming linearity in the potential relationships. A goodness-of-fit chi-square value with $P_{\text{goodness-of-fit}}$ was calculated to test the suitability of the model.

To identify the potential modifiers, the stratified analyses were conducted by sex, smoking status, cases, study locations, and assessment of BMI, respectively. To further analyze the heterogeneity between eligible studies, sensitivity analysis was performed by ignoring a single study in turn. Potential publication bias was assessed by Begg rank-correlation test\cite{29} and Egger linear regression test.\cite{30} All analyses were conducted using STATA version12.0 (StataCorp, College Station, TX). $P < .05$ was considered statistically significant.

3. Results

3.1. Literature search
The flow of literature search exhibited in Fig. 1. Electronic search identified 397 citations and 372 citations from PubMed and EMBASE, respectively. After removing duplications, 508 citations were identified. A total of 468 citations were excluded after reviewing their titles and abstracts, and 25 citations were included. Studies identified through database searching PubMed (n=627) EMBASE (n=372) Duplications removed (n=261) Studies for screening (n=950) Studies excluded after reviewing titles and abstracts (n=446) Relevant eligible studies (n=45) Excluded studies (n=39) Studies included in this meta-analysis (n=14)

Figure 1. The flowchart of selecting eligible studies.
## Table 1

Characteristics of included studies regarding BMI and mortality from lung cancer.

| Author/publication year, study location | Sample size | Mean follow-up, y | Cases | BMI categories (kg/m²) | Ascertainment of death | Assessment of weight and height | Adjustment factors |
|----------------------------------------|-------------|-----------------|-------|-----------------------|------------------------|-------------------------------|-------------------|
| Taghizadeh et al, 2015 [14], Netherlands | 8465        | 16              | 275   | <25; 25–30; 30        | NR                     | NR                            | Age, smoking habits, and place of residence, sex, age, survey, alcohol consumption, civil status, years of education, nationality, and healthy diet. |
| Meyer et al, 2015 [7], Switzerland     | 52,819      | 9               | 591   | <25; 25–30; >30       | NR                     | Self-reports                  | Age, marital status, race/ethnicity, nativity, education, poverty status, home ownership, and region of residence. |
| Siahpush et al, 2013 [8], USA          | 52,819      | 9               | 591   | <25; 25–30; >30       | NR                     | Questionnaire                 | Sex, smoking status, and variables. |
| Leung et al, 2011 [9], Hong Kong       | 64,574      | 7.18            | 932   | <18.5; 18.5–25; 25–30; ≥30 | Registry               | Questionnaire                 | Age, sex, smoking status, alcohol intake. |
| Leitzmann et al, 2011 [35], USA        | 225,712     | 8.71            | 2925  | 18.5–24.9; 25.0–29.9; 30.0–34.9 | National Death Index   | Height was measured using a stadiometer. Both were taken at least twice and recorded to the nearest millimetre to provide a mean. | Race/ethnicity, education attainment, family income level, marital status, and types of residence area, alcohol drinking, cigarette smoking, and frequency of eating fruit and vegetables. |
| Hotchkiss and Leyland, 2011 [32], Scotland  | 20,117      | 12              | 537   | <18.5; 18.5–25; 25–30; ≥30 | National Health Service administrative data | Weight was measured using electronic scales. Height was measured using a stadiometer. Both were taken at least twice and recorded to the nearest millimetre to provide a mean. | Age, smoking. |
| Parr et al, 2010 [27], Asia and Australia/New Zealand (ANZ) within the Asia Pacific South Carolina | 424,519     | 4               | 1478  | 12.0–18.4; 18.5–24.9; 25.0–29.9; 30.0–60.0 | National Death Index   | NR                            | Age, sex, years of education, occupation, hypertension, cigarette smoking. |
| Nonemaker et al, 2009 [11], UK         | 2054        | 4               | 101   | <25; 25–29; ≥29       | National Death Index   | NR                            | Age, geographical region, socioeconomic status, reproductive history, smoking status, alcohol intake, physical activity, and, where appropriate, time since menopause and use of hormone replacement therapy. |
| Reeves et al, 2003 [34], UK            | 12,00,000   | 7               | 3959  | <22.5; 22.5–24.9; 25–27.4; 27.5–29.5; ≥30 | National Health Service | Age and smoking risk factors | Age, alcohol consumption, body mass index, fasting serum glucose level, cholesterol level, physical activity, food preference, blood pressure, and other comorbidities. |
| Tsai et al, 2006 [35], USA             | 7139        | 20              | 116   | <25; 25–30; >30       | Social Security Administration's Death Master File | Height was measured with the subject wearing disposable foam rubber slippers; Weight was measured using a Toledo self-balancing scale | Age, plus employment grade, physical activity, smoking habit, marital status, disease at entry, weight loss in the last year, blood pressure-lowering medication, height adjusted FEV1, triceps skin-fold thickness, systolic blood pressure, plasma cholesterol, glucose intolerance, and diabetes status. |
| Cai et al, 2003 [27], USA               | 900,053     | 16              | 15,274| 18.5–24.9; 25.0–29.9; 30.0–34.9; 35.0–39.9; ≥40.0 | National Death Index   | NR                            | Age, education, smoking status and number of cigarettes smoked, physical activity, alcohol use, marital status, race, aspirin use, fat consumption, and vegetable consumption. |
| Li et al, 2002 [36], USA                | 6209        | 8               | 47    | <21.2; 21.2 to <23.6; 23.6 to ≥25.2; ≥25.2 | Medical record         | NR                            | Age, sex, smoking, and alcohol consumption. |

NDI = the National Death Index, NR = not report.
3.2. Study characteristics

The characteristics of 15 eligible researches are showed in Table 1. The included studies were published from 2002[31] to 2015,[7,14] five studies were conducted in Europe,[7,14,32–34] 6 in America,[2,8,11,13,35,36] and 4 in Asia.[9,31,37,38] The sample size ranged from 2054[11] to 1,200,000[33] across studies, and the mean follow-up years of included studies varied from 3 years[38] to 28.1 years.[14] Except for 1 article based on community,[9] others were all population-based.[2,7,8,11,13,14,31–38] This meta-analysis included 27,229 death cases after more than 200 million person-years. The most participants in eligible studies were diagnosed by International Classification of Disease (ICD) 9 or 10 codes. BMI in all the studies was calculated as weight in kilograms divided by the square of height in meters, which was assessed by self-reported,[8] questionnaire,[2,9,33,35] and objective text.[13,32,34]

As for quality assessment, 7 studies were found to be of high quality[2,9,13,32–35]; the others were considered of moderate quality, which indicated that the quality of these eligible studies was generally good.

3.3. Association of BMI and lung cancer mortality

A total of 15,191,571 subjects and 28,273 death cases from LC among 15 studies were eligible for the relationship between BMI and LC mortality risk, and pooled RR for every 5kg/m² increment was 0.94 (95% CI 0.92–0.96, n = 15) (Fig. 2), with evidence of high heterogeneity ($I^2 = 94.70\%$, $P_{\text{heterogeneity}} < .0001$). A nonlinear association (goodness-of-fit $\chi^2_{14} = 125.11$, $P_{\text{goodness-of-fit}} < .0001$, $P_{\text{nonlinearity}} < .0001$) (Fig. 3) was found between BMI and the risk of mortality from LC. Compared with higher BMI, lower BMI showed higher LC mortality risk, indicating obesity exerts a protective effect on LC-associated death risk. No heterogeneity among this fitted spline was found (heterogeneity $\chi^2_{49} = 524.84$, $P_{\text{heterogeneity}} < .0001$).

3.4. Subgroup analysis

Several subgroup analyses on association between an increment of 5kg/m² and the risk of mortality from LC were conducted. Among all subgroups, there was no modification effect and difference observed on the basis of sex, smoking status, number of cases, study location, country, follow-up duration, and assessment of weight and height (all $P_{\text{interaction}} > .05$) (Table 2). Nevertheless, female and smokers benefit from high BMI than male and nonsmoking people, respectively. Asian study also observed this obesity paradox.
3.5. Sensitivity analysis and publication bias

Sensitivity analysis by ignoring a single study in turn did not significantly change the total risk estimate of mortality of LC, which ranged from 0.94 (95% CI 0.92–0.96) to 0.96 (95% CI 0.95–0.97) (Supplementary Fig. 1, http://links.lww.com/MD/B824). Nevertheless, when omitting the study reported by Siahpush et al,[8] the risk value deviated to 0.96 (95% CI 0.95–0.97), implying a potential influence factor. No evidence of publication bias was found by both Egger test and Begg test (all P > .05) (Supplementary Fig. 2, http://links.lww.com/MD/B824).

4. Discussion

A nonlinear relationship between BMI and mortality from LC risk was detected in this dose–response meta-analysis. Those with higher BMI obtained better survival; however, underweight or normal BMI suffered inversely and significantly associated with risk of LC mortality. In other words, there is an obesity paradox, which was consistent with previous studies.[7–9,11,32,33,36,37]

High heterogeneity in quantitative synthesis was observed, which remained when conducting subgroup analyses. Nevertheless, fitted dose–response curve with no heterogeneity was also identified. The sample size of eligible study made a contribution to lack of consistence in pooled results, because it ranged from 6209[31] to 1,200,000.[43] Additionally, considering those LC patients who died from LC often after a long time, most of included studies[7–9,11,13,14,32,36,38] extracted participants based on a series of databases, contributing to the inconsistence of results. However, we failed to yielded homogenous results when conducting subgroup analyses by this factor.

The interactions of smoking status influenced this relationship, which is 1 of the most crucial confounding factors. A collaborative analysis of 57 prospective studies indicated BMI was associated inversely with respiratory disease and LC. In the interaction by smoker, they found that these inverse associations were much stronger for smokers than nonsmokers.[14] We yielded similar results in our subgroup analysis, suggesting that BMI is inversely associated with risk of mortality from LC among smokers, and failed to obtain the statistical outcome among nonsmokers. On one hand, smoking plays an interventional effect by causing weight loss[39] and by increasing LC or its poor prognosis risk.[40] On the other hand, it was illustrated that cotinine concentration in serum was higher among obese than among lean people, which is a biological LC carcinogen.[41]

| Table 2 |

Subgroup analyses regarding BMI and LC mortality.

| Subgroup                          | N  | RR (95% CI) | I² (%) | P heterogeneity | P interaction |
|-----------------------------------|----|-------------|--------|----------------|--------------|
| Sex                               |    |             |        |                |              |
| Male                             | 4  | 0.94 (0.89, 1.00) | 96.1   | .00            | .73          |
| Female                           | 3  | 0.93 (0.90, 0.96)  | 96.2   | .00            | /            |
| Smoking status                   |    |             |        |                |              |
| Never smoking                    | 2  | 0.95 (0.88, 1.02)  | 81.8%  | .02            | .31          |
| Smoking                          | 2  | 0.87 (0.79, 0.96)  | 92.2%  | .00            | /            |
| Adjusted smoking status          | 12 | 0.95 (0.94, 0.97)  | 85.6   | .00            | /            |
| No. of cases                     |    |             |        |                |              |
| >500                              | 8  | 0.93 (0.90, 0.96)  | 97.2   | .00            | .38          |
| <500                              | 7  | 0.97 (0.95, 0.99)  | 34.6   | .16            | /            |
| Study location                   |    |             |        |                |              |
| USA                              | 5  | 0.92 (0.84, 0.99)  | 91.3   | .00            | .52          |
| Europe                           | 6  | 0.97 (0.94, 0.99)  | 97.8   | .00            | /            |
| Asia                             | 4  | 0.91 (0.69, 1.2)   | 83.4   | .00            | /            |
| Follow-up duration               |    |             |        |                |              |
| ≥10 y                            | 7  | 0.96 (0.95,0.98)   | 48.3   | .00            | .24          |
| <10 y                            | 8  | 0.93 (0.89,0.96)   | 97.1   | .00            | /            |
| Assessment of weight and height  |    |             |        |                |              |
| Questionnaire                    | 4  | 0.96 (0.96, 0.97)  | 94.6   | .00            | .24          |
| Self-reported                    | 1  | 0.82 (0.80, 0.84)  | 0.00   | .00            | /            |
| Others                           | 3  | 0.97 (0.92, 1.02)  | 65.6   | .06            | /            |
| NR                               | 7  | 0.95 (0.92, 0.98)  | 69.55  | .00            | /            |
| Participants from databases      |    |             |        |                |              |
| Yes                              | 9  | 0.93 (0.87, 0.98)  | 95     | .00            | .26          |
| No                               | 6  | 0.96 (0.95, 0.98)  | 91.9   | .00            | /            |

BMI = body mass index, CI = confidence interval, N = number of study, RR = relative risk.
Additionally, sex, follow-up duration, and number of cases were taken into account, but no significant difference was found between every subgroup.

The plausible mechanisms on association of BMI and the risk of mortality from LC were unclear. Obesity may exert a protective effect on respiratory-related incident or its mortalities, including tuberculosis[12] and other respiratory mortalities.[4] Immunity-based theory was proposed, underlying immune surveillance enhancement could blind the truth.[9] Meanwhile, more number of people had increased exposure to potentially harmful environment, which may lead to the increased risk of death from LC.

The strength of this dose–response meta-analysis was to clarify the association and its shape between BMI and the risk of mortality from LC. To the best of our knowledge, we are the first to identify these. We employed the dose–response meta-analysis to achieve a reliable model, and various subgroup or sensitivity analyses were conducted to explore the potential confounding factors. Previous meta-analysis[6] also tried to address these issues, but categorical analyses showed deficiency of power. Most important, their study entitled “Premorbid body mass index and mortality in patients with LC: a systematic review and meta-analysis” was confused among subjects with LC or not. In fact, most of their included studies included cancer-free patients. In addition, our eligible studies were awarded moderate to high-quality assessment. Moreover, included studies had adjusted major confounders such as age, sex, smoking status, and so on. Prospective cohort studies have the advantage of less bias than case-control studies. Multiple studies published in recent 1 or 2 years have been included in our meta-analysis in an attempt to update and validate the associations.

Still, it will have some limitations. Firstly, we never tried to search unpublished studies, leading to missing relevant studies. Then, death certificate was used to ascertain the causes of death in some studies, which is inaccurate in some conditions.[45] Lastly, although we could not find any publication bias in Begg test and Egger test, the publication bias must exist in this meta-analysis.

5. Conclusions
This meta-analysis found a nonlinear association between BMI and the risk of LC mortality. Obesity or overweight have a low protective effect on respiratory-related incident or its mortalities, between every subgroup.

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