Reduced lung function predicts risk of incident type 2 diabetes: insights from a meta-analysis of prospective studies

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Abstract. Epidemiological studies have repeatedly investigated the association between reduced pulmonary function and incident type 2 diabetes mellitus (T2DM). However, the results have been inconsistent. This meta-analysis aimed to clarify this association with prospective cohort studies. We searched PubMed, Web of Science (ISI), and Google Scholar for all studies (in English) reporting reduced lung function with a risk of T2DM. The measures of lung function included percentage of forced vital capacity for predicted values (FVC%pre), percentage of forced expiratory volume in the first second after expiration for predicted values (FEV1%pre) and FEV1/FVC ratio%. Summary risk ratios (RRs) and 95% confidence intervals (CIs) were calculated using fixed-effects or random-effects meta-analyses. A total of 5,480 incident T2DM patients among 88,799 individuals were identified from nine prospective cohort studies. Compared to the highest category of FVC%pre and FEV1%pre, the lowest category of FVC%pre and FEV1%pre were significantly associated with increased incident T2DM risk (FVC%pre: RR = 1.49, 95% CI: 1.39–1.59; FEV1%pre: RR = 1.52, 95% CI: 1.42–1.62). However, no significant relationship was found between the FEV1/FVC ratio and incident T2DM risk (RR = 1.01, 95% CI: 0.91–1.13). Current evidence suggests that restrictive rather than obstructive impairment of lung function is significantly associated with the incidence of T2DM. Further research is warranted to explore potential mediators of this relationship.

Key words: Type 2 diabetes, Pulmonary function, Prospective studies

TYPE 2 DIABETES MELLITUS (T2DM) is a major public health concern that has reached epidemic levels worldwide, affecting 463 million people and accounting for 4.2 million deaths in 2019 [1]. Accumulating evidence [2, 3] suggests that reduced lung function might act as a predictor of T2DM incidence. However, the causal direction between reduced lung function and diabetes, as well as the underlying mechanism to explain this association, remains unclear [4–6]. Despite this ambiguous nature, the relationship between T2DM and lung function remains important because of potential epidemiological and clinical implications.

Prior meta-analyses and reviews [7, 8] have reported the association of T2DM and the risk of reduced pulmonary function but have not evaluated the association of impaired lung function with incident T2DM risk. Thus, in this meta-analysis, we aimed to systematically review the observational evidence available on the relationship between impairment of lung function and incident T2DM with prospective cohort studies.

Methods

Data sources and searches

A comprehensive search was performed for relevant English language articles through August 2020 using the following databases: (1) PubMed; (2) Web of Science (ISI); and (3) Google Scholar. The following search terms were used in combination: (“diabet*”) AND [“(FVC” OR “FVC%pre” OR “FEV1” OR “FEV1%pre” OR “FEV1-to-FVC ratio%” OR “lung function” OR “spirometry”) NOT (“cystic fibrosis” OR “COPD” OR “cancer”)] AND (“prospective” OR “cohort” OR “cohorts” OR “longitudinal” OR “follow-up”). In addition, we manually scanned and examined the reference lists in relevant articles. We followed standard criteria for conducting meta-analyses and reporting the results [9]. This meta-analysis was registered on PROSPERO (registration number CRD42021257570).
Study selection
Each identified study was independently reviewed by two investigators to determine whether an individual study was eligible for inclusion in this meta-analysis. The inclusion criteria were as follows: (1) prospective cohort studies; (2) the exposure of interest was FVC_{%pre} and/or FEV_{1%pre} and/or FEV_{1-to-FVC ratio}%; (3) the outcome of interest was incident T2DM; and (4) adjusted risk estimate with their 95% CI for two or more quantitative categories of FVC_{%pre} and/or FEV_{1%pre} and/or FEV_{1-to-FVC ratio}%. The highest categories were used as reference groups. In addition, case reports, editorials, reviews, animal studies or in-vitro researches were excluded. Besides, studies lacking relevant data also were excluded. When data from several publications were overlapping, we selected the publication with the most comprehensive data for inclusion in the meta-analysis.

Data extraction
Two authors (YP.Z. and M.W.) independently reviewed titles and abstracts of the potentially eligible articles and extracted the following information from the studies: the first author’s name, year of publication, country where the study was performed, sex, number of participants and incident cases, variables adjusted for in the analysis, as well as multivariate adjusted RRs and 95% CIs for measurements of T2DM. For studies that reported results from various covariates analyses, we abstracted the estimates based on the model that included the most potential confounders.

Quality assessment
The quality of the studies was evaluated with the Newcastle Ottawa Scale (NOS). This scale included eight items that judge three dimensions as follows: selection (score of 0–4), comparability (score of 0–2) and ascertainment of exposure or outcome (score of 0–3). The maximum score was nine stars, and studies with seven or more stars were considered as having a low risk of bias [10]. We chose this tool because it allowed us to appropriately adapt its domains for our exposure and outcome, it was validated for longitudinal studies [11], and the score of each study would be used to assess risk of bias as a potential moderator in meta-regression analyses [12, 13]. Two assessors independently rated each study, and consensus discussion was used to resolve any disagreement.

Statistical analysis
Pooled measure was calculated as the inverse variance-weighted mean of the natural logarithm of multivariate adjusted RRs with 95% CIs to assess the association of lung function and T2DM. The F was used to assess heterogeneity among studies [14], and described the proportion of total variation attributable to between-study heterogeneity as opposed to random error or chance. In the presence of substantial heterogeneity (I^2 > 50%) [15], the DerSimonian and Laird random effect model (REM) was adopted as the pooling method; otherwise, the fixed effect model (FEM) was used as the pooling method. Publication bias was estimated using Egger’s regression asymmetry test [16].

All statistical analyses were performed with STATA version 15 (Stata Corporation, College Station, Texas, USA). All reported probabilities (p values) were two-sided, with p < 0.05 considered statistically significant.

Results
A total of 1,597 studies were identified through the literature search. After review of the titles and abstracts, 1,555 studies were excluded and 42 studies were reviewed with the full texts. A total of nine studies [5, 17-24] were included in the final meta-analysis, comprising 88,799 individuals and 5,480 incident T2DM patients (Fig. 1).

Characteristics of the studies
The characteristics of the selected studies are outlined in Supplemental Table 1. The nine prospective studies, one study [21] was conducted in the United States, two in Europe [20, 22], and six in Asia [5, 17-19, 23, 24]. The sample sizes ranged from 2,967 to 27,711 and the mean age of the participants ranged from 41 to 60 years. Among the prospective studies, four [19, 21, 22, 24] reported two separate outcomes (men and women) on the association of reduced lung function and incident T2DM. All studies were assessed using the NOS with low risk of bias and high methodological quality. The quality criteria ranged from 7 to 8 stars in our study.

Reduced lung function and incident T2DM
Forced vital capacity (FVC) (% predicted)
Seven studies [5, 18, 19, 21-24] had 11 outcomes on the association of FVC_{%pre} with the risk of T2DM. Compared to the highest category of FVC_{%pre}, the lowest category of FVC_{%pre} was significantly associated with T2DM risk (RR = 1.49, 95% CI: 1.39–1.59, F = 0.0%, p_{heterogeneity} = 0.80) with no evidence of heterogeneity (Fig. 2). Egger’s test showed no evidence of publication bias (p = 0.77).

Forced expiratory volume in 1 second (FEV_{1}) (% predicted)
Six studies [5, 18, 21-24] had nine outcomes on the association of percent-predicted FEV_{1%pre} with risk of
T2DM. Compared to the highest category of FEV\(_{1%}\)pre, the lowest category of FEV\(_{1%}\)pre was significantly associated with T2DM risk (RR = 1.52, 95% CI: 1.42–1.62, \(I^2 = 0.0\%\), \(p_{\text{heterogeneity}} = 0.97\)) with no evidence of heterogeneity (Fig. 3). Egger’s test showed no evidence of publication bias (\(p = 0.09\)).

Forced expiratory volume in 1 second/forced vital capacity (FEV\(_1\)-to-FVC ratio%)

Five studies [5, 17, 19, 20, 22] with seven outcomes on the association of FEV\(_1\)-to-FVC ratio% with risk of T2DM. Compared to the highest category of FEV\(_1\)-to-FVC ratio%, the lowest category of FEV\(_1\)-to-FVC ratio%
was not significantly associated with T2DM risk (RR = 1.01, 95% CI: 0.91–1.13, \( I^2 = 15.9\% \), \( p_{\text{heterogeneity}} = 0.31 \), Fig. 4). Egger’s test showed no evidence of publication bias (\( p = 0.64 \)).

**Discussion**

We systematically reviewed and synthesized the available evidence on the association between reduced lung function and the risk of incident T2DM. Based on our results, reduced lung function measured with the percentage of FVC for predicted values (FVC\(_{\%}\text{pre} \)) and the percentage of FEV\(_1\) for predicted values (FEV\(_{1\%}\text{pre} \)) were significant risk factors for the development of T2DM. However, no significant relationship was found between the FEV\(_1\)-to-FVC ratio and the incident T2DM risk.

FVC, the total volume of air exhaled with maximally forced effort from a maximal inspiration, reflects the total compliance from both the lung and chest wall [25]. In most of the individual studies, reduced FVC and FVC\(_{\%}\text{pre} \) were significantly associated with increased incident T2DM risk. Compared with control participants, significantly higher increased odds of developing diabetes were observed in studies where participants were all males [5, 18, 26]. FEV\(_1\), the most frequently used spirometric index, is a function of airway resistance and total lung compliance [25]. Similar to FVC, a significant association was observed between lower FEV\(_1\) and FEV\(_{1\%}\text{pre} \) and incident T2DM in the overall meta-analysis.

The spirometric measurements of FVC\(_{\%}\text{pre} \) and FEV\(_{1\%}\text{pre} \) were used as markers of restrictive lung dysfunction. In addition, the FEV\(_1\)-to-FVC ratio\% is a marker of obstructive lung dysfunction [27]. In brief, this study suggests that restrictive rather than obstructive impairment of lung function is associated with T2DM, which is consistent with previous studies [17, 20]. Early detection and management of incident T2DM among patients with reduced lung function is needed. Recommendations to improve glycemic status and to control lipid metabolism in people with pulmonary dysfunction, e.g., low-intensity exercise and diet restriction, might be important in preventing T2DM incidence.

The interplay between T2DM and lung function was likely to be mediated through multiple mechanisms. Possible explanations for the association might include hypoxia-induced insulin resistance [28], chronic inflammation [29, 30], and lower levels of physical activity [22]. Chronic low-grade inflammation in the lungs might affect systemic inflammation through inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-a) and IL-6, into the systemic circulation [31], thereby contributing to an increase in insulin resistance. Taken together, the potential mechanisms are complex and might involve several shared physiological pathways, such
as obesity and inflammation. Certainly, more studies are needed to explore the mechanisms underlying this relationship, which would be crucial for the prevention and treatment of T2DM.

The strength of this study was that this meta-analysis explicitly examined the relationship of lung function and T2DM on the basis of a comprehensive literature search. The large number of participants and T2DM cases could provide higher statistical power with which to quantitatively assess the relationship of reduced lung function and T2DM compared with individual studies [32]. However, as a meta-analysis of published observational studies, several potential limitations should also be considered. First, all studies included had no experimental manipulation, and consequently this research was unable to address the causal relationship between lower lung function and T2DM. Nonetheless, the present data is important because they might be among the strongest forms of evidence ethically possible. Second, misclassification of T2DM status (fasting glucose level, a self-reported medical history of type 2 diabetes, or oral glucose tolerance tests) might also lead to an underestimation of the true magnitude of the associations. Third, the categories of the indicators of lung function might slightly differ between studies, which might complicate the interpretation of the pooled results across study populations with different categories. A dose-response analysis between lung function and T2DM would provide a more robust method to combine results from individual studies and better quantify the relationship between lung function and T2DM. Thus, further prospective studies eligible for the dose-response meta-analysis are warranted.

Despite these limitations, our results still have important implications for both clinical care and public health. The existing literature indicates that restrictive rather than obstructive impairment of lung function confers an increased risk of T2DM outcomes, which should inform guidelines and practice. In addition, more studies are needed to evaluate whether early screening and collaborative care for patients with reduced lung function could reduce the future risk of T2DM.

**Key Messages**

- Previous epidemiology studies have shown inconsistent associations between lung dysfunction and the risk of T2DM.
- The study indicated a significant association between reduced lung function and T2DM. These results support early detection and management of incident T2DM among patients with reduced lung function.
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Conflicts of Interest

None.

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