Association of iron deficiency anemia with tuberculosis in Taiwan: A nationwide population-based study

Kuo-An Chu¹,²,³☯, Chun-Hsiang Hsu¹☯, Mei-Chen Lin⁴, Yi-Hsin Chu⁵, Yao-Min Hung⁶,⁷,⁸*, James Cheng-Chung Wei⁹,¹⁰,¹¹,¹²*

¹ Division of Chest Medicine, Department of Internal Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, ² Department of Nursing, Shu-Zen Junior College of Medicine and Management, Kaohsiung, Taiwan, ³ School of Medicine, National Yang Ming University, Taipei, Taiwan, ⁴ Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan, ⁵ Department of Family Medicine, National Cheng Kung University Hospital, Tainan, Taiwan, ⁶ Kaohsiung Municipal United Hospital, Kaohsiung, Taiwan, ⁷ Department of Emergency Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, ⁸ Yuhing Junior College of Health Care and Management, Kaohsiung, Taiwan, ⁹ Department of Rheumatology, BenQ Medical Center, The Affiliated BenQ Hospital of Nanjing Medical University, China, ¹⁰ Institute of Medicine, Chung Shan Medical University Hospital, Taichung, Taiwan, ¹¹ Department of Medicine, Chung Shan Medical University Hospital, Taichung, Taiwan, ¹² Graduate Institute of Integrated Medicine, China Medical University, Taichung, Taiwan

☯ These authors contributed equally to this work.
* ymhung1@gmail.com (YMH); jccwei@gmail.com (JCCW)

Abstract

Background
Iron deficiency is associated with decreased cellular immunity, which may predispose patients with iron deficiency anemia (IDA) to increased risk of developing tuberculosis (TB). This study investigated the relationship between newly diagnosed IDA and TB infection in Taiwan.

Methods
The study included data on 21,946 patients with incident IDA and 87,555 non-IDA controls from a national database covering the period 2000–2012. IDA and non-IDA subjects were matched 1:4 on age, gender, and index year. The follow-up period was defined as the time from the initial IDA diagnosis to the date of developing TB or 31 December 2013. Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals, with the control group as the reference.

Results
The adjusted hazard ratio of TB for the IDA group was 1.99 (95% confidence interval, 1.77–2.25) compared with the control group. The subgroup analysis showed that for both genders, all age groups, and patients with diabetes mellitus, hyperlipidemia, hypertension, cancer, chronic obstructive pulmonary disease, and hepatitis B virus infection, the IDA group had significantly higher TB incidence. The association was significantly stronger within the 5 years after new IDA diagnosis for both genders and all age groups.
Conclusions

Higher TB incidence was discovered in the IDA group, especially for patients with comorbidities.

Introduction

Tuberculosis (TB), an infectious disease caused by *Mycobacteria tuberculosis*, is characterized by tubercle bacilli displaying intracellular survival strategies and chronic pulmonary inflammation [1]. The global burden of TB is still increasing, and the morbidity and mortality of TB remain substantial [2]. In 2012, approximately 8.6 million new cases of TB and an estimated 1.3 million related mortalities were reported globally [3]. TB affected approximately 10.4 million people and caused 1.7 million deaths worldwide in 2016 [4]. Preventing TB infection is thus a crucial global health issue. TB is endemic and highly prevalent in Taiwan. In 2012, the incidences of TB and TB-related death were 53 and 2.7 cases per 100,000 individuals, respectively [5]. Researchers have been searching for more means of preventing new cases of TB [2]. An assessment of potentially modifiable risk factors is a promising consideration for the formulation of TB control policies [6]. Some TB risk factors have been known for decades, including systemic diseases such as diabetes mellitus (DM) [7] and chronic kidney disease [8] as well as tobacco smoking [9], alcohol use [10], body mass index [11], silicosis [12], human immunodeficiency virus (HIV) infection [13], splenectomy [14], and gastrectomy [15,16]. Most of these risk factors can impair the human immune system, thereby increasing the risk of TB. However, few studies have investigated the link between nutritional iron deficiency and high TB prevalence.

Micronutrient deficiencies are a well-known global health threat, and poor nutritional status may predispose an individual to some infectious diseases [17]. Anemia, a critical global health problem, is the most common micronutrient deficiency, occurring in approximately one quarter of the world’s population [17,18]. Iron deficiency anemia (IDA) is the most significant contributor, accounting for 50% of all cases of anemia. IDA has a prevalence of 2%–5% among adult men and postmenopausal women in the developed world [19]. Animal and human studies have demonstrated that nutritional iron deficiency is associated with impaired phytohemagglutinin-induced lymphocyte proliferation and delayed-type hypersensitivity responses with relative preservation of humoral immunity [20–25].

TB and IDA are major public health concerns worldwide. Nonetheless, the relationship between iron deficiency, especially IDA, and the risk of contracting TB remains unclear. By using data in the Taiwan National Health Insurance Research Database (NHIRD) for the period January 1, 2000, to December 31, 2012 in the current population-based cohort study, we examined the association between newly diagnosed IDA and subsequent TB development.

Material and methods

Study design

This study is a retrospective matched-cohort study analyzing data over a period of 12 years in a nationwide, population-based database in Taiwan.

Database

The IDA and control cohorts were created using the Taiwan NHIRD, which is maintained by a single national health insurance (NHI) program that covered 99.6% of Taiwan’s population.
until 2011. The NHIRD contains patient demographic information, encrypted identification number, gender, birth date, diagnostic data and procedures, all types of medical visits (outpatient department, emergency care, and hospitalizations), traditional Chinese medical services, and prescription drug use. The diagnostic and procedure codes are based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The Longitudinal Health Insurance Database 2000 (LHID 2000), a subset of the NHIRD, was employed in this study. The LHID 2010 is composed of all original claims data of 1,000,000 randomly sampled beneficiaries of the NHI program. No significant differences in age distribution, gender, or health care cost were noted between the 1,000,000 people in the LHID 2010 and the individuals in the NHIRD.

Study population
Cases of IDA and TB were identified from the NHIRD by using the corresponding ICD-9 codes 280.X and 011–018, respectively, for the period from January 2000 to December 2012. We first identified patients with newly diagnosed IDA from data concerning both outpatient and inpatient visits. IDA was defined through diagnostic ICD codes and procedure codes, including complete blood count tests and serum ferritin tests. The index date was defined as the first date of IDA diagnosis. For further ascertainment, only patients with at least one inpatient admission or three outpatient visits during the 1 year after IDA was first diagnosed were selected. We then excluded patients who had previous history of TB (ICD-9-CM 010.x to 018.x and anti-TB drugs for 2 months), those <20 years of age, and those who withdrew from the insurance program before the index date. The IDA group finally comprised 21,946 patients. The non-IDA control group was randomly selected from the patients who had never been diagnosed with IDA or TB (selected at a 1:4 ratio matched by age, gender, and index year). The non-IDA control group comprised 87,555 people. Individuals in both groups were tracked until a TB event, withdrawal from the NHI program, or the end of 2013, whichever occurred first.

Covariables
Factors that might influence the incidence of TB—such as age, gender, income level, and comorbidities—were used as independent variables. We classified age into three groups: 20–39, 40–64, and ≥65 years. The comorbidities analyzed in this study were hypertension (ICD-9-CM codes 401–405), DM (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), chronic obstructive pulmonary disease (COPD; ICD-9-CM codes 491, 492, 496), cancer (ICD-9-CM codes 140–208), chronic kidney disease (CKD) (ICD-9-CM code 585), alcoholic liver disease (ICD-9-CM 571.0, 571.1, 571.3), liver cirrhosis (ICD-9-CM code 571.4), hepatitis B (ICD-9-CM codes 070.2, 070.3, V02.61), hepatitis C (ICD-9-CM codes 070.41, 070.44, 070.51, 070.54, V02.62), HIV infection (ICD-9-CM code 042–044 795.8 V08), pneumoconiosis (ICD-9-CM code 042–044 795.8 V08), splenectomy (ICD-9-CM procedure code 41.5), partial gastrectomy (ICD-9-OP 43.5, 43.6, 43.7, 43.8, 43.81, 43.82, 43.89), and total gastrectomy (ICD-9-OP 43.91 and 43.99). Information on comorbidities was obtained by tracing all ambulatory medical care and inpatient records in the NHI database for the 2 years before the index date.

Outcome measurement
Regarding outcomes, we focused on the development of *Mycobacterium tuberculosis* infection. Diagnosis of TB was identified using ICD-9-CM codes 010–018 in combination with the prescription of at least two anti-TB drugs within 6 months of TB diagnosis.
Statistical analysis

Proportional differences in independent variables between the IDA and control cohorts were analyzed using the Pearson $\chi^2$ test. The incidence of TB was expressed as the number of newly diagnosed TB cases per 10,000 person-years. To assess the risk of subsequently developing TB, we performed Cox regression analysis to obtain the crude and adjusted hazards ratios (HRs) and 95% confidence intervals (CIs) for the case group compared with the control group. Cox regression models were adjusted for age, gender, and all comorbidities. Furthermore, we performed stratified analysis by calculating the HRs for the patients with IDA according to different subgroups. The significance level was set to a two-tailed $p$ value of 0.05. All data analyses were performed using SAS$^\text{R}$ (version 9.4; SAS Institute, Inc., Cary, NC, USA).

This study was approved by the Institutional Review Board of China Medical University (permit number: CMUH-104-REC2-115-R3). Because all data were used anonymously and fully deidentified before analysis, the need for informed consent was waived by the board.

Results

Overall, 413 individuals in the IDA group (which comprised 21,946 patients) developed newly onset TB during the follow-up period. The longest follow-up period was 8 years. Overall, the crude TB infection rate, which is the crude HR (95% CI), was 1.94 (1.73–2.17) for the IDA group.

Demographic characteristics and comorbidities of patients with newly diagnosed IDA and the comparison cohort in Taiwan during 2000–2012

Table 1 displays the clinical characteristics of the patients with and without IDA. IDA was more prevalent in women than men (72.3% vs. 27.7%). The mean age at time of IDA diagnosis was 53.6 years. Comorbidities were more common in the IDA group.

Risk factors of new-onset TB among the patients with IDA and comparison cohort

Table 2 presents the results of univariate and multivariate Cox regression analyses. Among all of the relevant variables, being in the IDA cohort, age > 40 years, male gender, gastrectomy, and comorbidities of DM, chronic kidney disease, COPD, pneumoconiosis, liver cirrhosis were the risk factors associated with a higher risk of developing TB. The crude HR (95% CI) for the IDA group was 1.94 (1.73–2.17). After adjustment for age, gender, and comorbidities, the risk of developing TB was similar (aHR, 1.99; 95% CI, 1.77–2.25). The survival curve (Fig 1) shows that the cumulative incidence of TB was higher in the IDA cohort than in the comparison group ($p < 0.0001$).

Incidence rate, HR, and CI of TB in different subgroups

Table 3 reveals the association of risk of TB between gender, age, and comorbidity subgroups. In the gender-subgroup analysis, both men and women with IDA had higher TB risk than those without IDA. In all age groups, the IDA group had a higher risk of TB than the comparison group. In different stratifications of baseline comorbidities, the patients with DM, hyperlipidemia, hypertension, cancer, COPD, or hepatitis B virus infection in the IDA group had a significantly higher risk of TB. For the patients with hepatitis B virus infection, the IDA group had a 5.98-fold higher risk of TB (95% CI, 2.5–14.32).
Table 4 details the incidence and HR of TB stratified by follow-up years. In the analysis of the three age subgroups, the aHR (95% CI) of TB for the IDA group was the highest and most significant in the first 2 years, at 3.33 (1.61–6.88), 2.59 (1.75–3.84), and 2.15 (1.72–2.69) in the 20–39, 40–64, and ≥65 years age groups, respectively (p < 0.001). In all age subgroups, IDA was associated with higher incidence of subsequent TB, especially within the first 2 years after IDA diagnosis; even 5 years after IDA diagnosis, these patients were more likely to develop TB. In the 40–64 years age subgroup, the patients with IDA exhibited a significantly increased association with TB compared with the comparison group even after ≥5 follow-up years.

Discussion

In this nationwide population-based study of data covering 12 years, we discovered that people with new diagnoses of IDA were nearly twice as likely to subsequently develop TB than those without IDA. Overall, IDA was associated with a 99% increased incidence of TB compared with the matched group. This result supports the hypothesis that individuals with iron deficiency are more susceptible to infections, perhaps because of impaired cell-mediated immunity. Furthermore, the effects of IDA were found to be more significant in some high-
risk groups, such as patients with DM, hyperlipidemia, hypertension, cancer, COPD, or hepatitis B virus infection. Age is also another consideration for the prevention of TB among those with newly diagnosed IDA. Age had effects on both the strength and duration of the TB association.

To the best of our knowledge, this is the first large-scale study to assess the association of newly diagnosed IDA with subsequent TB. Our study is unique for several reasons. First, the sample size of the current study was large (enrolling 109,501 patients overall) and the follow-up period (131,326.7 person-years for the IDA cohort) was longer than in all other studies investigating the incidence of TB for various subgroups of patients with anemia. This strength enabled us to analyze the association of IDA with TB in groups stratified by age, gender, comorbidities, and follow-up period. Second, our data were obtained from a national insurance database covering a whole country with a single ethnic population; thus, the results are superior to those in smaller, single-hospital, and specific age or gender studies and those using purposive sampling [26,27]. This strength minimized potential bias from the sampling process [28]. Third, we defined IDA and TB by using accurate diagnosis criteria. IDA cases were defined using both ICD codes and procedure codes, whereas TB diagnosis was defined using both ICD codes and prescription codes for at least two anti-TB drugs.

### Table 2. Cox-model–measured hazard ratio and 95% confidence interval of tuberculosis associated with iron deficiency anemia in patients.

| Characteristics                  | Event (n = 1361) | Person year | IR | Crude HR (95% CI) | Crude p value | Adjusted HR (95% CI) | Adjusted p value |
|----------------------------------|------------------|-------------|----|-------------------|---------------|----------------------|------------------|
| Iron deficiency anemia           | No               | 948         | 589070 | 16.09             | Ref.          | Ref.                 |                  |
|                                  | Yes              | 413         | 131327 | 31.45             | 1.94(1.73–2.17) | <0.001              | 1.99(1.77–2.25)  | <0.001           |
| Gender                           |                  |             |       |                   |               |                      |                  |
| Female                           | 624              | 547074      | 11.41 | Ref.              |               | Ref.                 |                  |
| Male                             | 737              | 173322      | 42.52 | 3.64(3.28–4.06)   | <0.001        | 2.04(1.83–2.29)     | <0.001           |
| Age at baseline                  |                  |             |       |                   |               |                      |                  |
| 20–39                            | 85               | 201705      | 4.21  | Ref.              |               | Ref.                 |                  |
| 40–64                            | 359              | 342640      | 10.48 | 2.48(1.95–3.14)   | <0.001        | 2.21(1.74–2.81)     | <0.001           |
| ≥65                              | 917              | 176051      | 52.09 | 12.03(9.62–15.03) | <0.001        | 7.55(5.9–9.65)      | <0.001           |
| Baseline comorbidity             |                  |             |       |                   |               |                      |                  |
| Hypertension                     | 773              | 207254      | 37.30 | 3.16(2.84–3.52)   | <0.001        | 1.02(0.9–1.17)       | 0.75             |
| Diabetes mellitus                | 398              | 100892      | 39.45 | 2.45(2.18–2.76)   | <0.001        | 1.23(1.08–1.41)      | 0.002            |
| Hyperlipidemia                   | 398              | 141213      | 28.18 | 1.64(1.46–1.85)   | <0.001        | 0.8(0.7–0.91)        | <0.001           |
| Chronic kidney disease           | 89               | 13095       | 67.96 | 3.54(2.85–4.39)   | <0.001        | 1.38(1.1–1.72)       | 0.01             |
| Cancer                           | 441              | 240071      | 18.37 | 0.94(0.84–1.05)   | 0.27          | 0.89(0.79–1)         | 0.05             |
| COPD                             | 479              | 82567       | 58.01 | 4.05(3.62–4.53)   | <0.001        | 1.75(1.55–1.98)      | <0.001           |
| Alcoholic liver disease          | 20               | 4254        | 47.02 | 2.38(1.53–3.70)   | <0.001        | 1.38(0.87–2.17)      | 0.17             |
| Liver cirrhosis                  | 56               | 8448        | 66.29 | 3.38(2.58–4.42)   | <0.001        | 1.53(1.15–2.05)      | 0.004            |
| Hepatitis B                      | 24               | 16922       | 14.18 | 0.71(0.48–1.07)   | 0.10          | 0.62(0.41–0.94)      | 0.02             |
| Hepatitis C                      | 34               | 7658        | 44.40 | 2.25(1.60–3.16)   | <0.001        | 1.15(0.8–1.64)       | 0.46             |
| HIV infection                    | 1                | 139         | 71.79 | 3.54(0.50–25.00)  | 0.20          | 2.77(0.39–19.77)     | 0.31             |
| Pneumoconiosis                   | 43               | 4666        | 92.16 | 4.72(3.48–6.40)   | <0.001        | 1.66(1.22–2.25)      | 0.001            |
| Splenectomy                      | 2                | 364         | 54.87 | 2.71(0.68–10.83)  | 0.16          | 1.34(0.33–5.44)      | 0.68             |
| Gastrectomy                      | 16               | 1699        | 94.15 | 4.81(2.94–7.88)   | <0.001        | 1.74(1.05–2.87)      | 0.03             |

HR, hazard ratio; CI, confidence interval.

* Adjusted HR: adjusted for gender, age, and all comorbidities in the Cox proportional hazards regression.

https://doi.org/10.1371/journal.pone.0221908.t002
The study data revealed that compared with the general population, patients with IDA had a greater incidence of subsequent TB development. The overall TB risk of the patients with IDA was higher than that of general population (aHR, 1.99 [95% CI, 1.77–2.25]), with an aHR (95% CI) of 2.02 (1.72–2.39) and 1.96 (1.64–2.33) for men and women, respectively. In addition, we identified some high-TB-risk groups of patients with IDA. Patients with DM, hyperlipidemia, hypertension, cancer, COPD, or hepatitis B virus infection in the IDA group were significantly more likely to develop TB. For the patients with hepatitis B virus infection, the IDA group had a 5.98-fold higher association with TB (95% CI, 2.5–14.32).

Another finding of this study that deserves attention is the effect of age on the TB association and the duration of the association. For all age groups, the IDA group had a stronger association with TB than the comparison group. However, as age increased, the association with TB infection became weaker. The aHR (95% CI) of TB association decreased from 2.75 (1.75–
4.33) in the 20–39 years subgroup to 1.83 (1.57–2.13) in the ≥65 years subgroup. In all age subgroups, IDA was associated with higher incidence of subsequent TB, especially in the first 2 years after IDA diagnosis. Even 5 years after IDA diagnosis, these patients were still more likely to develop TB. However, only in the 40–64 subgroup, patients with IDA exhibited a significantly higher association with TB than the comparison group even after ≥5 follow-up years.

Several reasons may explain why more young patients with IDA developed TB. First, younger people tend to exhibit more symptoms and thus may be more likely to receive a TB diagnosis. Second, it is more likely for older people to be lost to follow-up than younger people with IDA because several years may have passed since their IDA diagnosis. After several years of follow-up, they may have also been eating iron-rich foods or independently taking drugs rather than visiting a doctor to obtain such drugs. This may have resulted in older patients with IDA being less frequently recorded in the NHIRD database.

The present findings have both clinical and public health implications. Clinically, physicians and patients should be aware of the possible association between TB and IDA. When treating patients with IDA and DM, hyperlipidemia, hypertension, cancer, COPD, or hepatitis B virus infection, clinicians must be aware of the increased risk of TB incidence. From a public
health perspective, policymakers can consider implementing a TB screening test for certain high-risk patients with IDA.

Some limitations should be noted. Determining a strong association between IDA and TB by using a diagnosis database is extremely difficult and potentially uncertain. First, the diagnoses of IDA and TB in this study were mainly based on diagnostic ICD codes from insurance claims data rather than medical record review, which may have caused misclassification bias. To improve diagnostic validity, IDA cases were identified through diagnostic ICD codes and procedure codes and TB cases through both diagnostic ICD codes and prescription codes. In Taiwan, diagnosis of anemia is primarily based on complete blood count; when doctors determine that the complete blood count reveals microcytic anemia, they order further laboratory testing on serum iron, ferritin, and TIBA. IDA diagnoses are made when serum ferritin levels are low. In addition, diagnosis of TB in Taiwan is based on culture and image findings but sometimes through tissue biopsy and pathological findings. Second, data on alcohol consumption, smoking, homosexual or bisexual behaviors, malnutrition, socioeconomic status, body mass index, and severity of iron deficiency are unavailable in the NHIRD and are all potential confounding factors of TB. Consequently, we could not adjust for these variables and conduct related analysis. To partially address this, we used COPD as a proxy variable for cigarette smoking, similar to some other studies [29–31]. Third, our longitudinal follow-up study demonstrated an association but not a causal relationship. Moreover, we could not determine whether the etiology, severity, and duration of IDA were related to the development of TB. Further studies concerning whether IDA severity is related to TB infection rate should be conducted. Finally, IDA is more common in women; thus, our sample is not representative of the global TB population; moreover, most Taiwanese people have Chinese ethnicity, and our findings therefore may not be generalizable to other racial groups. Our results, therefore, should be cautiously interpreted.

Table 4. Incidence and hazard ratio of tuberculosis with stratification by follow-up year.

| Variables               | Control | Case | Case VS. Control |
|-------------------------|---------|------|------------------|
| n = 87,555              | n = 21,946 |      |                  |
| Event                  | Person years | IR | Event | Person years | IR | (95% CI) | (95% CI) |
| Patients less than aged 40 years |         |      |        |              |    |          |          |
| <2                     | 17 | 42128 | 4.04 | 16 | 10454 | 15.30 | 3.80(1.92–7.51) | 3.33(1.61–6.88) |
| ≥5                     | 21 | 68527 | 3.06 | 13 | 16862 | 7.71 | 2.52(1.26–5.03) | 1.98(0.93–4.19) |
| Patients aged 40–64 years |       |      |        |              |    |          |          |
| <2                     | 62 | 75810 | 8.18 | 52 | 18173 | 28.61 | 3.50(2.42–5.06) | 2.59(1.75–3.84) |
| ≥5                     | 92 | 112750 | 8.16 | 33 | 24919 | 13.24 | 1.63(1.10–2.43) | 1.57(1.04–2.36) |
| Patients more than aged 65 years |       |      |        |              |    |          |          |
| <2                     | 246 | 50040 | 49.16 | 122 | 10807 | 112.89 | 2.27(1.83–2.82) | 2.15(1.72–2.69) |
| ≥5                     | 221 | 51345 | 43.04 | 77 | 9370 | 82.18 | 1.91(1.47–2.48) | 1.81(1.39–2.36) |
| IR, incidence rates, per 10,000 person-years; HR, hazard ratio; CI, confidence interval. |
| a Adjusted HR: adjusted for gender, age, and all comorbidities in Cox proportional hazards regression. |
| b p < 0.05 |
| c p < 0.01 |
| d p < 0.001 |

https://doi.org/10.1371/journal.pone.0221908.t004
Conclusion

This 12-year nationwide population-based cohort study determined that patients with newly diagnosed IDA had increased incidence of subsequent TB, regardless of gender and age. Age had effects on both the strength and duration of the TB association. Future studies are required to explore the mechanisms underlying these associations. Clinicians are suggested to be aware of the higher TB risk of patients with new IDA diagnosis and to provide appropriate monitoring of high-risk groups.

Acknowledgments

Acknowledgments to Wallace Academic Editing company for their English editing.

Author Contributions

Conceptualization: Kuo-An Chu, Chun-Hsiang Hsu, Mei-Chen Lin, Yi-Hsin Chu, Yao-Min Hung, James Cheng-Chung Wei.

Data curation: Mei-Chen Lin.

Formal analysis: Kuo-An Chu, Chun-Hsiang Hsu, Mei-Chen Lin, Yi-Hsin Chu, Yao-Min Hung, James Cheng-Chung Wei.

Funding acquisition: Mei-Chen Lin.

Investigation: Kuo-An Chu, Yao-Min Hung, James Cheng-Chung Wei.

Writing – original draft: Kuo-An Chu, Chun-Hsiang Hsu, Yao-Min Hung.

Writing – review & editing: Yao-Min Hung, James Cheng-Chung Wei.

References

1. Wang SH, Chung CH, Huang TW, Tsai WC, Peng CK, Huang KL, et al. Bidirectional association between tuberculosis and sarcoidosis. Respirology. 2019 Feb 5. https://doi.org/10.1111/resp.13482 PMID: 30722101

2. Davies PD. The world-wide increase in tuberculosis: how demographic changes, HIV infection and increasing numbers in poverty are increasing tuberculosis. Ann Med. 2003; 35:235–43. PMID: 12846265

3. World Health Organization. Global tuberculosis report 2013.

4. World Health Organization. Tuberculosis. Available online: http://www.who.int/mediacentre/factsheets/fs104/en/index.html. (accessed on 17 Jan 2019).

5. Su VY, Su WJ, Yen YF, Pan SW, Chuang PH, Feng JY, et al. Statin use is associated with a lower risk of TB. Chest 2017; 152: 598–606. https://doi.org/10.1016/j.chest.2017.04.170 PMID: 28479115

6. GBD Tuberculosis Collaborators. The global burden of tuberculosis: results from the Global Burden of Disease Study 2015. Lancet Infect Dis. 2018 Mar; 18(3):261–84. https://doi.org/10.1016/S1473-3099(17)30703-X PMID: 29223583

7. Jeon C Y, Murray M B. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. PLOS Med 2008; 5: e152. https://doi.org/10.1371/journal.pmed.0050152 PMID: 18630984

8. Min J, Kwon SK, Jeong HW, Han JH, Kim YJ, Kang M, et al. End-stage Renal Disease and Risk of Active Tuberculosis: a Nationwide Population-Based Cohort Study. J Korean Med Sci. 2018 Dec 13; 33 (53):e341. https://doi.org/10.3346/jkms.2018.33.e341 PMID: 30959682

9. Lin H H, Ezatti M, Murray M. Tobacco smoke, indoor air pollution and tuberculosis: a systematic review and meta-Analysis. PLOS Med 2007; 4: e20. https://doi.org/10.1371/journal.pmed.0040020 PMID: 17227135

10. Lonnroth K, Williams B G, Stadlin S, Jaramillo E, Dye C. Alcohol use as a risk factor for tuberculosis—a systematic review. BMC Public Health 2008; 8: 289. https://doi.org/10.1186/1471-2458-8-289 PMID: 18702821
11. Lonnroth K, Williams B G, Cegielski P, Dye C. A consistent loglinear relationship between tuberculosis incidence and body mass index. Int J Epidemiol 2010; 39: 149–55 https://doi.org/10.1093/ije/dyp308 PMID: 19820104

12. Barboza C E, Winter D H, Seiscente M, Santos Ude P, Terra Filho M. Tuberculosis and silicosis: epidemiology, diagnosis and chemoprophylaxis. J Bras Pneumol 2008; 34: 959–66 https://doi.org/10.1590/s1806-37132008001100012 PMID: 19099104

13. Getahun H, Gunneberg C, Granich R, Nunn P. HIV infection associated tuberculosis: the epidemiology and the response. Clin Infect Dis 2010; 50 (Suppl 3): S201–S207

14. Lai SW, Wang IK, Lin CL, Chen HJ, Liao KF. Splenectomy correlates with increased risk of pulmonary tuberculosis: a case–control study in Taiwan. Clin Microbiol Infect. 2014 Aug; 20(8):764–7 https://doi.org/10.1111/cmi.12516 PMID: 24372744

15. Cheng KC, Liao KF, Lin CL, Lai SW. Gastrectomy correlates with increased risk of pulmonary tuberculosis: A population-based cohort study in Taiwan. Medicine (Baltimore). 2018 Jul; 97(27):e11388.

16. Steiger Z, Nickel WO, Shannon GJ, Nedwicki EG, Higgins RF. Pulmonary tuberculosis after gastric resection. Am J Surg. 1976 Jun; 131(6):668–71. https://doi.org/10.1016/0002-9610(76)90174-4 PMID: 937642

17. Maggini S, Pierre A, Calder PC. Immune Function and Micronutrient Requirements Change over the Life Course. Nutrients. 2018 Oct 17; 10(10). pii: E1531. https://doi.org/10.3390/nu10101531 PMID: 30336639

18. Camaschella C. Iron-deficiency anemia. N. Engl. J. Med. 2015; 372:1832–43. https://doi.org/10.1056/NEJMra141038 PMID: 25946282

19. DeLoughery T G. Microcytic anemia. N. Engl. J. Med. 2014; 371:1324–31. https://doi.org/10.1056/NEJMra1215361 PMID: 25271605

20. Ganz T. Iron and infection. Int J Hematol. (2018) Jan; 107(1):7–15. https://doi.org/10.1007/s12185-017-2366-2 PMID: 29147843

21. Oppenheimer SJ. Iron and its relation to immunity and infectious disease. J Nutr.2001 ; 131: 616S–635S. https://doi.org/10.1093/jn/131.2.616S PMID: 11160594

22. Macdougall IG, Anderson R, McNab GM, Katz J. The immune response in iron-deficient children: impaired cellular defense mechanisms with altered humoral components. J Pediatr. 1975; 86: 833–43. https://doi.org/10.1016/s0022-3476(75)80211-3 PMID: 1127523

23. Laut Freddie J. Haemoglobin levels are associated with bone mineral density in the elderly : A population-based study. Clin. Rheumatol. 2009; 28:145–51. https://doi.org/10.1007/s10067-008-0998-6 PMID: 18766424

24. Korkmaz U, Korkmaz N, Yazici S, Erkan M, Baki A.E, Yazici M. Anemia as a risk factor for low bone mineral density in postmenopausal Turkish women. Eur. J. Intern. Med.2012 ; 23:154–58. https://doi.org/10.1016/j.ejim.2011.11.009 PMID: 22284246

25. Pan ML, Chen LR, Tsao HM, Chen KH. Iron Deficiency Anemia as a Risk Factor for Osteoporosis in Taiwan: A Nationwide Population-Based Study. Nutrients. 2017 Jun 16; 9(6). pii: E616 https://doi.org/10.3390/nu9060616 PMID: 28621741

26. Chang KH, Chang MY, Muo CH, Wu TN, Chen CY, Kao CH. Increased risk of dementia in patients exposed to nitrogen dioxide and carbon monoxide: a population-based retrospective cohort study. PloS one. 2014; 9(8):e103078 https://doi.org/10.1371/journal.pone.0103078 PMID: 25115393

27. Raaschou P, Simard JF, Asker Hagelberg C, Asking J. Rheumatoid arthritis, anti-tumour necrosis factor treatment, and risk of squamous cell and basal cell skin cancer: cohort study based on nationwide prospectively recorded data from Sweden. BMJ. 2016; 352:i262 https://doi.org/10.1136/bmj.i262 PMID: 26823527

28. Chang KH, Hsu YC, Hsu CC, Lin CL, Hsu CY, Lee CY, et al. Prolong Exposure of NSAID in Patients With RA Will Decrease the Risk of Dementia.Medicine (Baltimore). 2016; 95(10):e3056.